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Stereoselective Organocatalytic Synthesis of Oxindoles with Adjacent Tetrasubstituted Stereocenters**

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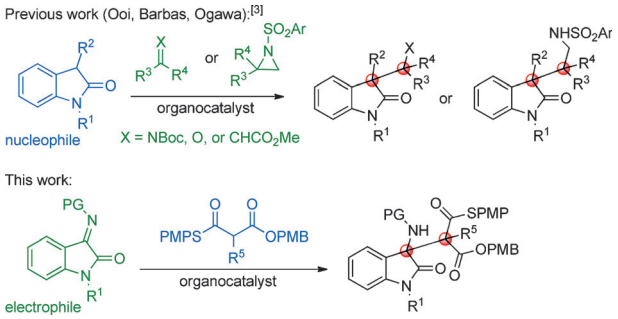
In memory of Gerhard Quinkert

Abstract: *Oxindoles with adjacent tetrasubstituted stereocenters were obtained in high yields and stereoselectivities by organocatalyzed conjugate addition reactions of monothiomalonates (MTMs) to isatin-derived N-Cbz ketimines. The method requires only a low catalyst loading (2 mol%) and proceeds under mild reaction conditions. Both enantiomers are accessible in good yields and excellent stereoselectivities by using either Takemoto's catalyst or a cinchona alkaloid derivative. The synthetic methodology allowed establishment of a straightforward route to derivatives of the gastrin/cholecystokinin-B receptor antagonist AG-041R.*

The catalytic stereoselective synthesis of compounds with adjacent tetrasubstituted stereogenic centers is one of the most difficult tasks in organic synthesis.[1] It is particularly challenging when at least one center is part of an acyclic moiety since their formation is then highly aggravated by the rotational freedom and steric congestion upon C–C bond formation.[1] Oxindoles with substituents at C3 contain this structural motif and are part of several natural products and bioactive molecules.[2] Thus, there is a need for mild, organocatalytic methods that enable the construction of oxindoles with fully substituted vicinal stereogenic centers where one is part of an acyclic moiety. This task has been achieved by the groups of Ooi, Barbas, and Ogawa by utilizing the nucleophilicity of enolates derived from C3-substituted oxindoles (Scheme 1, top).[3] Use of oxindoles as the electrophilic part would considerably broaden the scope of accessible oxindole derivatives with this structural motif (Scheme 1, bottom). Despite intense research on additions to oxindole derivatives[4] this has proven to be difficult and only allowed for the formation of oxindoles with fully substituted stereogenic centers that are part of cyclic structures.[5,6]

In recent years, malonic acid half thioesters (MAHTs) have become popular as thioester enolate equivalents in organocatalytic decarboxylative C–C bond-forming reactions.[7] We advanced this methodology by introducing monothiomalonates (MTMs), which allowed the organocatalytic synthesis of addition products bearing quaternary stereogenic centers with high stereoselectivities.[8] These findings encouraged us to explore whether addition reactions of MTMs allow access to compounds with vicinal tetrasubstituted stereocenters.



Scheme 1. Synthetic routes to oxindoles with adjacent acyclic and cyclic tetrasubstituted stereocenters. Boc = *tert*-butoxycarbonyl, PG = protecting group, PMB = *para*-methoxybenzyl, PMP = *para*-methoxyphenyl.

Herein we present highly stereoselective syntheses of oxindoles with adjacent fully substituted cyclic and acyclic stereogenic centers that proceed under mild organocatalytic conditions. Enantiomeric addition products with orthogonally addressable functional groups for further derivatization were obtained in excellent stereoselectivities. Furthermore we show the synthetic value of the differentially functionalized oxindoles for the synthesis of derivatives of the bioactive β-amino-acid AG-041R.

We started by investigating conjugate addition reactions of the α-methyl MTM **1a** with isatin-ketimines under previously established reaction conditions and used cinchona alkaloid/(thio)urea derivatives[9] as catalysts (Scheme 2).[8] Initial experiments revealed that N-Boc ketimines react only sluggishly, whereas N-Cbz ketimines showed excellent conversion rates. Testing of a range of different bifunctional catalysts revealed that the addition product **3a** forms in high yield (94%) and with excellent stereoselectivity (d.r. > 20:1, > 99% *ee*) in the presence of only 2 mol% of the *epi*-cinchonidine urea **A** (Scheme 2 and the Supporting Information for details). Remarkably, the enantiomeric product *ent*-**3a** formed in equally high yield and stereoselectivities upon using Takemoto's catalyst (**B**).[10,11] It is also noteworthy that only a small excess (1.2 equiv) of the MTM was necessary to obtain these results.

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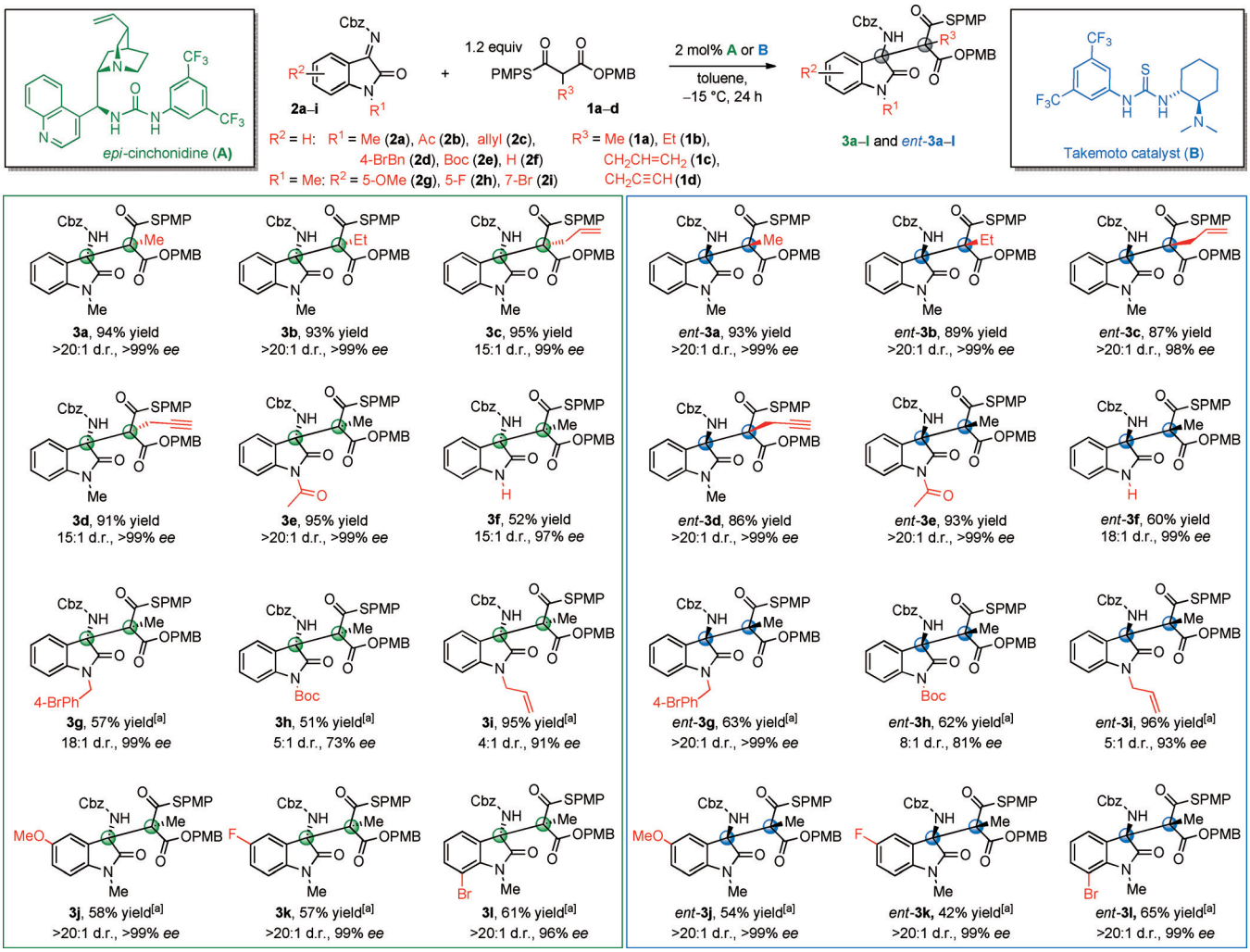
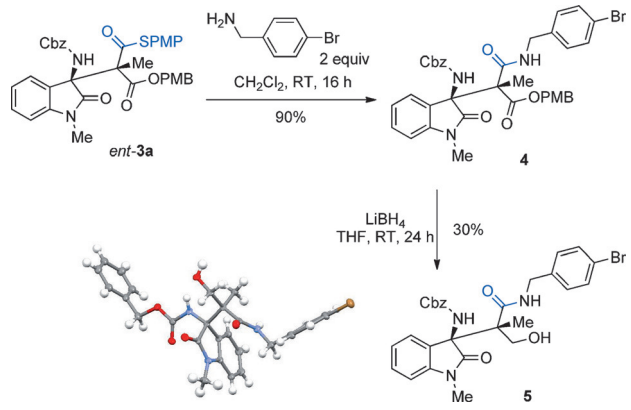


Scheme 2. Conjugate addition reaction between the MTMs **1a–d** and isatin-ketimines **2a–i**. Reactions were performed on a 0.2 mmol scale. Yields correspond to addition products isolated as a mixture of diastereoisomers. Enantioselectivities of the major diastereoisomers were determined by HPLC on a chiral stationary phase. Diastereoselectivities were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. The absolute configuration was determined after derivatization (Scheme 3). [a] Yields over two reaction steps, including the in situ generation of the ketimines **2c–i** by an aza-Wittig reaction from the respective isatin derivative. Cbz = benzyloxycarbonyl.

Next, we evaluated the scope of the conjugate additions and reacted different combinations of α-substituted MTMs (**1a–d**) with the isatin-ketimines **2a–i** in the presence of either **A** or **B** (Scheme 2). We were pleased to find that variations of the substituents at $C_{(\alpha)}$ of the MTM as well as at N1 and the benzene moiety of the isatin-ketimines were readily tolerated. The desired addition products were generally obtained in yields greater than 85% if the isatin-ketimines were sufficiently stable to be purified before the conjugate addition reaction was performed (**3a–f** and *ent*-**3a–f**). Several isatin-ketimines were not isolated after their preparation by aza-Wittig reactions but used in situ for conjugate addition reactions (see the Supporting Information for details). These addition products (**3g–3l** and *ent*-**3g–l**), which were formed in the presence of the Wittig reaction byproducts, were generally still obtained over two reaction steps in yields of greater than 50%. The adjacent fully substituted stereocenters typically formed with diastereoselectivities of greater than 15:1 and enantioselectivities of greater than 96% *ee* with both bifunctional catalysts. Even a bulky Boc group at N1 of the isatin was tolerated and provided **3h** and *ent*-**3h** with d.r. $\geq$ 5:1 and $\geq$ 73% *ee*.[12] The reaction of the unprotected isatin-ketimine **2f** provided the conjugate addition products **3f** and *ent*-**3f** in moderate yields but excellent stereoselectivities (d.r. $\geq$ 15:1, *ee* $\geq$ 97%), thus indicating that a competing hydrogen-bond donor reduces the activity of the catalysts but not their stereoselectivity.

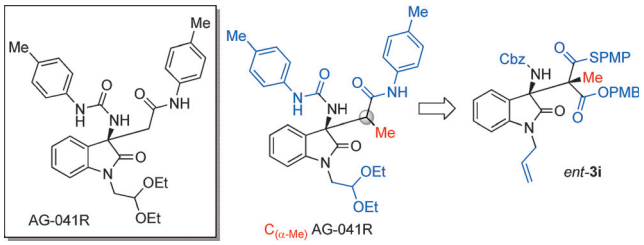
Molecular crowding at adjacent fully substituted carbon atoms can reduce the reactivity of the attached functional groups. To probe whether the differentially addressable oxo- and thioester moieties can be further functionalized we reacted *ent*-**3a** with 4-bromobenzylamine, which exclusively reacted with the thioester group to afford the amide **4** (Scheme 3). Subsequent selective reduction of the oxoester moiety provided the alcohol **5**, which crystallized and allowed the unambiguous assignment of the absolute and relative



Scheme 3. Selective functionalization of the thioester and oxoester moieties of *ent*-**3a** and crystal structure of **5**. THF = tetrahydrofuran.

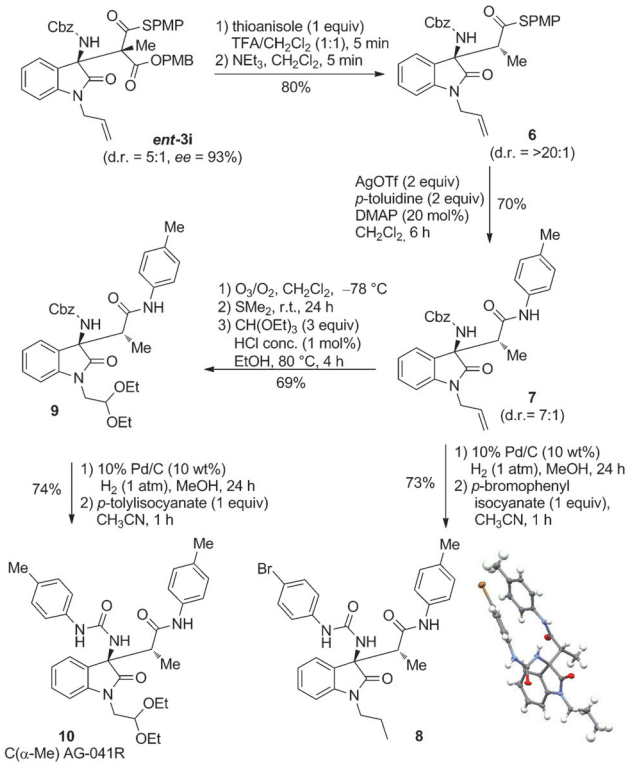
stereochemistry of the addition products (see the Supporting Information for details).

Finally, we probed the synthetic versatility of the conjugate addition products for the synthesis of previously inaccessible derivatives of the bioactive 3-amino-2-oxindole AG-041R.[13,14] This clinical candidate has attracted considerable attention as a gastrin/cholecystokinin-B receptor antagonist[14] and has systemically chondrogenic[15] and anticancer[16] activities. Whereas several methods for the synthesis of AG-041R[7c,17] are available, there is no route to expand this β-amino-acid-derived scaffold by additional substitution at $C_{(\alpha)}$. This substitution can be valuable since, for example, the stereoselective introduction of methyl groups is often a powerful tool for enhancing the activity of therapeutics by reducing their degrees of conformational freedom.[18] We envisioned that derivatization of the conjugate addition product *ent*-**3i** would allow the facile synthesis of $C_{(\alpha\text{-Me})}$ AG-041R derivatives (Scheme 4).



Scheme 4. Retrosynthesis of the $C_{(\alpha\text{-Me})}$ AG-041R derivative.

We commenced our synthesis by removal of the *p*-methoxybenzyl (PMB) protecting group from the oxoester moiety of *ent*-**3i** with TFA/CH_2Cl_2 in the presence of thioanisole as a nucleophilic scavenger (Scheme 5).[19] The deprotection was then followed by a base-promoted decarboxylation. The oxindole **6** was obtained as a single diastereomer (> 20:1 d.r.), which showed that the decarboxylation proceeded under substrate control and highly stereoselectively. Note, that both **3f** and *ent*-**3f** had been obtained with comparatively poor diastereoselectivities of only 5:1 d.r.,



Scheme 5. Synthesis of the $C_{(\alpha\text{-Me})}$ AG-041R derivative **10**. DMAP = 4-(*N*,*N*-dimethylamino)pyridine, TFA = trifluoroacetic acid, Tf = trifluoromethanesulfonyl.

which was compensated by the highly stereoselective decarboxylation. The relative and absolute configuration of **6** was determined by derivatization to the oxindole **8** for which the stereochemistry was unambiguously assigned by X-ray crystallography (see the Supporting Information for details). Silver-promoted amidation[20] of the thioester moiety within **6** in the presence of DMAP afforded the amide **7** with a small erosion of the diastereoselectivity (7:1 d.r.) at $C_{(\alpha\text{-Me})}$. Ozonolysis of the N-allyl moiety, followed by a reductive work up and subsequent transformation of the aldehyde into the diethyl acetal afforded **9**. Cleavage of the N-Cbz group with 10% Pd/C under an H_2 atmosphere (1 atm) and subsequent coupling of the resulting free amine with *p*-tolylisocyanate provided the $C_{(\alpha\text{-Me})}$ AG-041R derivative **10** in an overall yield of 27% over eight steps.

In conclusion, we have developed an operationally simple route to access 3-substituted 3-amino-2-oxindoles containing adjacent cyclic and acyclic tetrasubstituted stereocenters in high yields and excellent stereoselectivities. The reactions proceed under mild organocatalytic conditions, thus requiring low catalyst loadings of only 2 mol% and allow access to a broad variety of orthogonally functionalizable oxindoles. The choice of catalyst allows the selective formation of both enantiomers of the addition products. We have furthermore showcased the value of the methodology in a concise and highly stereoselective route to $C_{(\alpha\text{-Me})}$-substituted derivatives of the gastrin/cholecystokinin-B receptor antagonist AG-041R.

Experimental Section

General method of organocatalyzed conjugate addition reaction: The isatin-derived N-Cbz ketimine (1.0 equiv) was dissolved in toluene (0.2 M) and MTM (1.2 equiv) was added. The reaction mixture was cooled to −15 °C and the catalyst (0.02 equiv) was added. The mixture was shaken (ca. 5 s) and left standing at −15 °C (freezer, monitored with an external thermometer) for 24 h. The reaction mixture was warmed to RT and was quenched by immediate filtration through a short silica plug (eluting with EtOAc) to remove the catalyst. The resulting crude reaction mixture was purified by flash chromatography on silica, eluting with EtOAc/*n*-pentane to afford the product. Conjugate addition products **3g–l** and *ent*-**3g–l** were prepared without isolation of the ketimines, which were prepared by an aza-Wittig reaction (see the Supporting Information for full details).

Keywords: asymmetric synthesis · enantioselectivity · heterocycles · organocatalysis · synthetic methods

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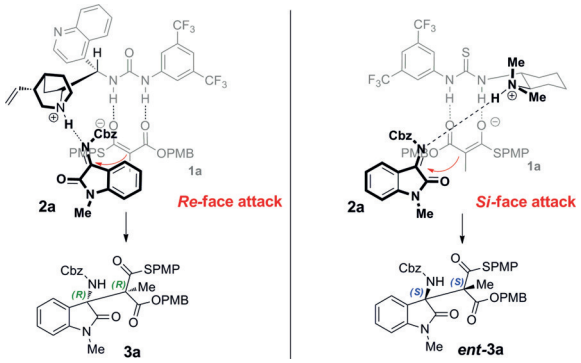

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