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# Control of N-Heterocyclic Carbene Catalyzed Reactions of Enals: Asymmetric Synthesis of Oxindole-γ-Amino Acid Derivatives

*Xiang-Yu Chen, Jia-Wen Xiong, Qiang Liu, Sun Li, He Sheng, Carolina von Essen, Kari Rissanen, and Dieter Enders**

***Abstract:*** *A strategy to control the switch between a non-cycloaddition reaction and a cycloaddition reaction of enals, using N-heterocyclic carbene (NHC) catalyisis, has been developed. The new scalable protocol leads to γ-amino-acid esters bearing a tetrasubstituted stereocenter in good yields and high stereoselectivities by homo-Mannich reactions of enals and isatin-derived ketimines. By simply changing the N-ketimine substituent to an ortho-hydroxy phenyl group, the corresponding spirocyclic oxindolo-γ-lactams are obtained.*

Compounds such as γ-amino acids and their derivatives have been widely applied in studies of various pathological conditions in the central nervous system, including Parkinson, Huntington, and Alzheimer diseases,[1] and they present important synthetic challenges. Their synthesis has fascinated many research groups and tremendous efforts have been devoted to the development of asymmetric strategies of enantioenriched γ-amino acids.[2] While a variety of synthetic protocols have been developed over the years for the synthesis of structurally diverse enantiopure γ-amino acids, to date, only rare examples exist for the preparation of enantioenriched tetrasubstituted γ-amino acids (Scheme 1 a). The groups of Dixon[3] and Jørgensen[4] have independently described a catalytic alkylation reaction with aziridines to prepare α,α-disubstituted γ-amino acids by phase-transfer catalysis. Later, a homodinuclear Ni₂/Schiff base was employed for their synthesis.[5] Kudo and co-workers developed a chiral peptide catalyzed Michael addition of nitroalkanes to enals as a key step for the preparation of β,β-disubstituted γ-amino acids.[6] A recent example involving the Michael addition of carbonyl compounds to nitroolefins was also realized by the groups of Wennemers[7] and Song,[8] respectively. Despite this progress, the catalytic asymmetric synthesis of γ,γ-disubstituted γ-amino acids has so far not been realized,[9] and the development of a practical, enantioselective synthetic route allowing various substitution patterns is thus highly desirable.

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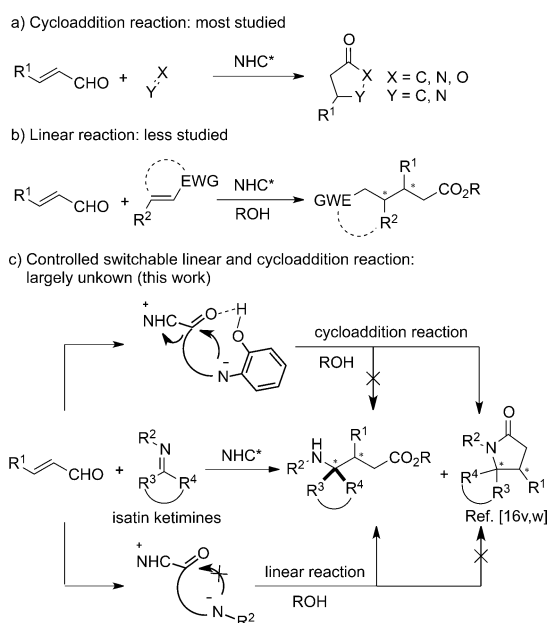
**Scheme 1.** Motivation.

3-Amino-oxindoles are an important class of pharmaceutically relevant compounds because of their prominent and wide-ranging biological activities, including the potent gastrin/CCK-B receptor antagonist AG-041R,[10] a HIV protease inhibitor,[11] and the vasopressin VIb receptor antagonist SSR-149415[12] (Scheme 1 b). The synthesis of hybrid molecules with more than one pharmacological property has gained momentum recently.[13] In this regard, combining the features of amino-oxindoles and γ-amino acids in a single molecule are expected to increase the diversity of pharmaceuticals with new pharmacological activities.

The homo-Mannich reaction is an efficient strategy for the synthesis of γ-amino acids,[14] however, considerable challenges still exist in developing catalytic asymmetric variants of this reaction. We envisioned that this could be accomplished by N-heterocyclic carbene (NHC) catalysis. N-heterocyclic carbene catalyzed processes, via homoenolate equivalent intermediates, have become a powerful strategy for enantioselective C–C bond formations.[15] Much effort has been focused on a variety of cycloaddition reactions for the preparation of cyclic compounds (Scheme 2 a).[16] In contrast, the corresponding asymmetric non-cycloadditive reactions of a linear substrates (referred to hereafter as linear reactions) are very limited, involving only two types of enantioselective homo-Michael addition reactions (Scheme 2 b).[15q] In 2012 and 2013, the groups of Liu and Rovis independently reported a chiral NHC-catalyzed homoenolate addition of enals to nitroalkenes for the synthesis of δ-nitro esters.[17] Very recently, the protocol was expanded to the reactions with alkyl pyridiniums by Rovis and co-workers.[18] Despite this progress, there is no efficient strategy to control the switch between a linear and cycloaddition reaction so far.[19] This idea is conceptually simple, but examining the pathway revealed several challenges to realizing it. The competing

**Scheme 2.** NHC-catalyzed asymmetric linear and cycloaddition reactions by homoenolate Mannich addition. EWG = electron-withdrawing group.

| Entry | Solvent | Base | Yield [%][a] | d.r.[b] | ee [%][c] |
|-------|---------|------|----------|------|--------|
| 1 | DME | K$_2$CO$_3$ | 84 | 8:1 | 85 |
| 2 | toluene | K$_2$CO$_3$ | 76 | 7:1 | 92 |
| 3 | THF | K$_2$CO$_3$ | 74 | 7:1 | 94 |
| 4 | 2-MeTHF | K$_2$CO$_3$ | 85 | 10:1 | 95 |
| 5[d] | 2-MeTHF | K$_2$CO$_3$ | 83 | 6:1 | 88 |
| 6[e] | 2-MeTHF | K$_2$CO$_3$ | 91 | 2:1 | 49 |
| 7 | 2-MeTHF | Cs$_2$CO$_3$ | 56 | 7:1 | 75 |
| 8 | 2-MeTHF | KHCO$_3$ | 83 | 6:1 | 90 |
| 9[f] | 2-MeTHF | K$_2$CO$_3$ | n.r. | – | – |

[a] Yield of the isolated product **3 a** after chromatography. [b] The d.r. values were determined by ^{1}H NMR analysis. [c] The *ee* value was determined by HPLC analysis of the purified product using a chiral stationary phase. [d] 1.0 equiv K$_2$CO$_3$ was used. [e] The reaction was carried out at RT. [f] No methanol was added. DME = 1,2-dimethoxyethane, M.S. = molecular sieves, THF = tetrahydrofuran.

*Table 2:* Stereoselective homo-Mannich reaction with various enals.



**3a**, X = H, d.r. = 10:1, 86%, 95% *ee*
**3b**, X = MeO, d.r. = 8:1, 92%, 96% *ee*
**3c**, X = Br, d.r. = 10:1, 75%, 90% *ee*
**3d**, X = F, d.r. = 9:1, 75%, 94% *ee*

**3e**, d.r. = 11:1, 82%, 91% *ee*

**3f**, d.r. = 6:1 90%, 91% *ee*

**3g**, d.r. = 6:1 58%, 86% *ee*

**3h**, R = Me, d.r. = 20:1, 63%, 96% *ee*
**3i**, R = *n*Bu, d.r. = 20:1, 59%, 94% *ee*

Yields of isolated products **3** after chromatography. The d.r. value was determined by ^{1}H NMR analysis and the *ee* value was determined by HPLC analysis of the purified product using a chiral stationary phase.

cycloaddition reactions will lead neither to linear products nor an uncontrollable mixture. Thus, Michael acceptors are usually needed for the linear reaction to suppress the cycloaddition process, because of the difficulty of regenerating the NHC catalyst through either nucleophilic attack of a carbon atom or using sterically hindered substrates to stop the cycloaddition process. This means if the linear reaction worked well, it would not be easy to switch the linear reaction to the cycloaddition mode because of the difficulty in regenerating the NHC catalyst by intramolecular acylation, or the interruption of the cycloaddition process by an additive. Herein we present a controlled switchable strategy for NHC-catalyzed asymmetric linear and cycloaddition reactions, and a concise catalytic asymmetric route to γ,γ-disubstituted γ-amino esters by highly stereoselective, NHC-catalyzed homo-Mannich reactions (Scheme 2c).

Initially, the model reaction of the enal **1a** and isatin-derived ketimine **2a** was investigated under NHC catalysis[16w] (Table 1). We were pleased to find that the reaction catalyzed by the NHC **A**,[20] in the presence of K$_2$CO$_3$ as the base, furnished the desired oxindole-γ-amino ester **3a** in 84% yield with 85% *ee* and 8:1 d.r. (entry 1). After optimization (entries 2–8), the result was improved to 85% yield with 10:1 d.r. and 95% *ee* when the reaction was carried out in 2-MeTHF (entry 4). No reaction was observed without methanol (entry 9).

With the optimized reaction conditions in hand, the scope of the enals was briefly investigated (Table 2). Both electron-donating (4-MeO) and electron-withdrawing (4-Br and 4-F) groups on the phenyl ring were tolerable and afforded the desired products **3b–d** in good yields and diastereomeric ratios with high enantioselectivities. The *ortho*-substituent (2-MeO) was also tolerated in the reaction without apparent change in the yield and enantioselectivity (**3e**). The reaction

of (*E*)-3-(furan-2-yl)acrylaldehyde gave the desired product **3f** in 90% yield with a 6:1 d.r. and 91% *ee* value. Notably, β-alkenyl enal also worked well in the reaction albeit in somewhat decreased yield (**3g**). The β-alkyl enals **1h** and **1i** were also successful and provided the desired products in moderate yields with excellent stereoselectivities.

A variety of substituted isatin ketimines were next evaluated under the optimal reaction conditions (Table 3). The isatin ketimines with electron-donating (4-Me, 3-Me and

2-Me) or withdrawing (4-F, 4-Cl, 4-Br, 3-Cl and 3-Br) groups on the phenyl group led to the corresponding products **3j–q** in good yields with good diastereoselectivities and high enantioselectivities. The absolute configuration of **3p** was determined by the X-ray structure analysis[21] and the configurations of all other products were assigned accordingly.

Furthermore, the electronic nature of the substituents on the backbone of the oxindole had no significant effect on the stereoselectivity, neither electron-withdrawing nor electron-donating groups. For example, the 5-Br-, 5-Me-, and 5-MeO-substituted isatin ketimines all worked well and gave the desired products with excellent enantioselectivities (**3r–t**; Table 3). Excellent stereoselectivities were also obtained with the introduction of a substituent at position 7 of the isatin ketimines (**3u**). The isatin ketimines with varying nitrogen protecting groups were also suitable reaction partners for the homo-Mannich reaction. N-phenyl isatin ketimine gave good yield of the product **3v**, with excellent stereoselectivity. A slight decrease in diastereoselectivity was observed with the isatin ketimine bearing a *p*-methoxyphenyl protecting group
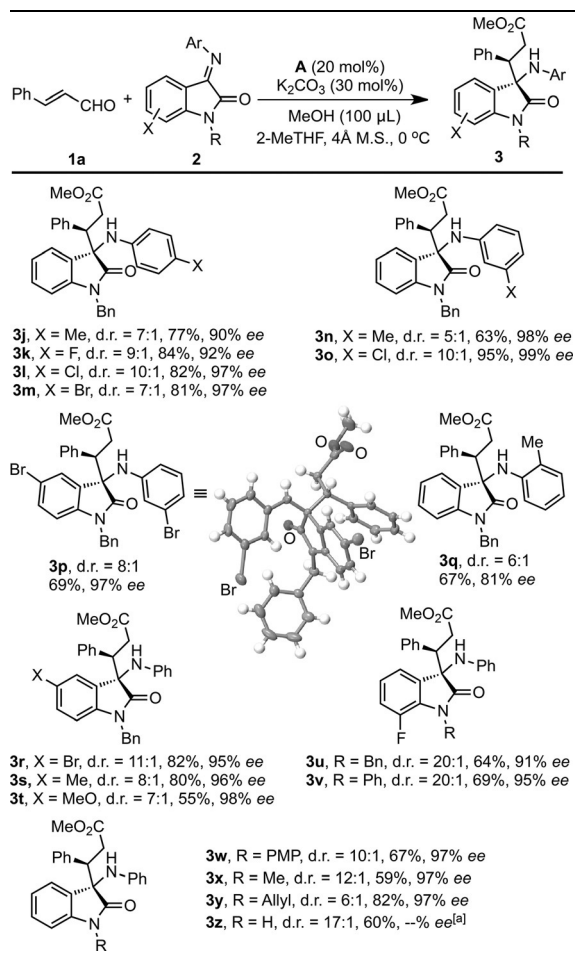
(**3w**). Gratifyingly, N-methyl and allyl isatin ketimines reacted smoothly as well to give the desired products **3x,y** in good yields and excellent enantioselectivities. It is notable that the N-unprotected substrate also worked well (**3z**).

This homo-Mannich process is not limited to the construction of γ-amino methyl esters. The corresponding ethyl esters could be obtained in the presence of ethanol in good yields and high enantioselectivities as well (**3a′**: 58 %, d.r. = 11:1, 96 % *ee* and **3m′**: 62 %, d.r. = 8:1, 85 % *ee*). Needless to mention that the new protocol is scalable to gram amounts (see the Supporting Information).

In contrast to the well-developed cycloaddition reactions via homoenolates, processes of switchable linear and cycloaddition reactions are still quite underdeveloped and challenging. Elegant asymmetric [3+2] cycloaddition reactions of isatin ketimines with enals have been achieved by Chi and coworkers.[16v] By introducing an *ortho*-hydroxy group to the ketimines, we were able to switch the linear reaction to the cycloaddition process. After optimizing the reaction conditions (see Table S1 in the Supporting Information), we successfully established the NHC-catalyzed [3+2] cycloaddition of enals with the *ortho*-hydroxy isatin ketimine **2b** by using the NHC, derived from **A**, as the catalyst (Table 4). The cycloaddition reaction worked as well, even in the presence of MeOH. Enals with electron-donating (4-Me) and electron-withdrawing groups (4-Br) reacted smoothly to give the corresponding spirocyclic oxindolo-γ-lactams **4b** and **4c** in good yields with good enantioselectivities. The *para*-N$_3$ substituted enal was readily accommodated under the standard reaction conditions (**4d**). The reaction of a substrate with a 2-furyl group also worked, thus providing the product **4e** in 60 % yield with 12:1 d.r. and 87 % *ee*. Notably, the β-alkyl enal **1f** also worked well in the reaction.

*Table 3:* Stereoselective homo-Mannich reaction with various isatin-derived ketimines.



**3j**, X = Me, d.r. = 7:1, 77%, 90% *ee*
**3k**, X = F, d.r. = 9:1, 84%, 92% *ee*
**3l**, X = Cl, d.r. = 10:1, 82%, 97% *ee*
**3m**, X = Br, d.r. = 7:1, 81%, 97% *ee*

**3n**, X = Me, d.r. = 5:1, 63%, 98% *ee*
**3o**, X = Cl, d.r. = 10:1, 95%, 99% *ee*

**3p**, d.r. = 8:1
69%, 97% *ee*

**3q**, d.r. = 6:1
67%, 81% *ee*

**3r**, X = Br, d.r. = 11:1, 82%, 95% *ee*
**3s**, X = Me, d.r. = 8:1, 80%, 96% *ee*
**3t**, X = MeO, d.r. = 7:1, 55%, 98% *ee*

**3u**, R = Bn, d.r. = 20:1, 64%, 91% *ee*
**3v**, R = Ph, d.r. = 20:1, 69%, 95% *ee*

**3w**, R = PMP, d.r. = 10:1, 67%, 97% *ee*
**3x**, R = Me, d.r. = 12:1, 59%, 97% *ee*
**3y**, R = Allyl, d.r. = 6:1, 82%, 97% *ee*
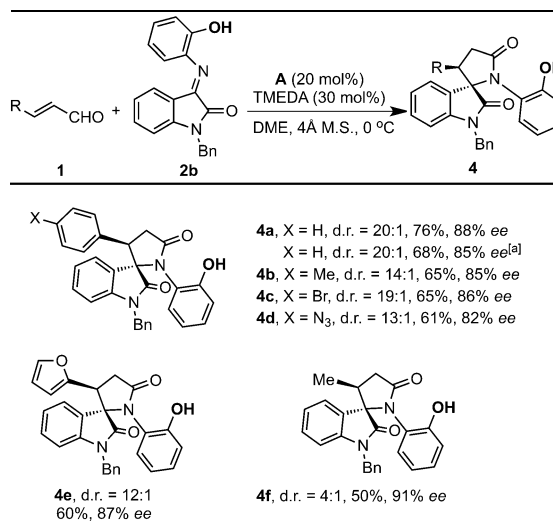**3z**, R = H, d.r. = 17:1, 60%, --% *ee*[a]

Yields of isolated products **3** after chromatography. The d.r. value was determined by $^1$H NMR analysis and the *ee* value was determined by HPLC analysis of the purified product using a chiral stationary phase. [a] We failed to determine the *ee* value because the two enantiomers could not be separated on the Daicel chiralpak columns.

*Table 4:* Stereoselective [3+2] cycloaddition of enals with isatin ketimine **2b**.



**4a**, X = H, d.r. = 20:1, 76%, 88% *ee*
   X = H, d.r. = 20:1, 68%, 85% *ee*[a]
**4b**, X = Me, d.r. = 14:1, 65%, 85% *ee*
**4c**, X = Br, d.r. = 19:1, 65%, 86% *ee*
**4d**, X = N$_3$, d.r. = 13:1, 61%, 82% *ee*

**4e**, d.r. = 12:1
60%, 87% *ee*

**4f**, d.r. = 4:1, 50%, 91% *ee*

Yields of isolated products **4** after chromatography. The d.r. value was determined by $^1$H NMR analysis and the *ee* value was determined by HPLC analysis of the purified product on a chiral stationary phase. [a] The reaction was carried out in the presence of 100 μL MeOH. TMEDA = *N,N,N′,N′*-tetramethylethylenediamine.

Based on the control experiments (see the Supporting Information), we propose possible pathways for this switchable asymmetric process (Figure 1). Firstly, the addition of the NHC to the enal gives the corresponding Breslow intermediate **I**, which then undergoes a homoaddition to the isatin ketimines **2** to generate the intermediate **II**. Tautomerization of **II** leads to the key intermediate **III**. In the presence of methanol the oxindole-γ-amino ester **3a** is generated by esterification and protonation. When the *ortho*-hydroxy group is present in the ketimine, it may be involved in the coordination to bring the nitrogen nucleophile into close proximity with the acyl azolium moiety by forming an intramolecular hydrogen bridge (**IV**). The intramolecular lactamization affords the oxindolo-γ-lactam **4a** and regenerates the NHC catalyst.
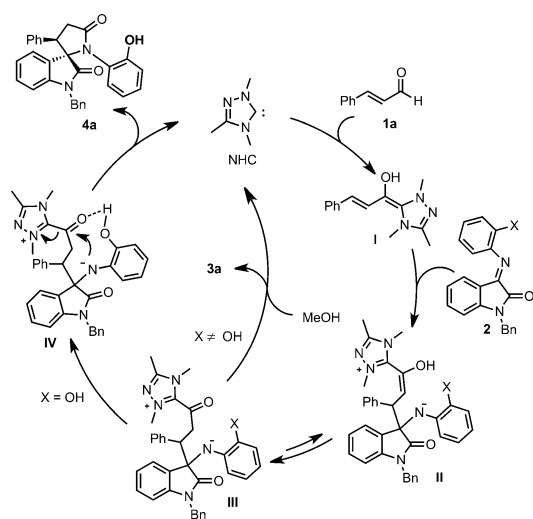


**Figure 1.** Plausible catalytic cycle.

In conclusion, we have developed a highly stereoselective NHC-catalyzed homo-Mannich reaction of enals with isatin ketimines. This protocol enables the efficient assembly of highly functionalized oxindole-γ-amino esters in good yields with high diastereoselectivities and excellent enantioselectivities. In addition, spirocyclic oxindolo-γ-lactams were successfully prepared by [3+2] cycloaddition of enals with *ortho*-hydroxy phenyl bearing isatin ketimines. The mild reaction conditions, the broad reaction scope, and the readily available substrates make this protocol potentially useful for the construction of highly substituted oxindole-γ-amino acid analogues.

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[21] CCDC 1571777 (**3p**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.