N-Heterocyclic Carbene-Catalyzed 1,6-Addition of Homoenolate Equivalent Intermediates: Asymmetric Synthesis of Nonspirocyclic Quaternary Oxindoles

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Although there is a growing interest in developing asymmetric 1,6-addition reactions of carbon nucleophiles to Michael acceptors, the corresponding 1,6-addition of homoenolates remains an unsolved problem. Currently, the N-heterocyclic carbene (NHC)-catalyzed cycloadditions of homoenolate equivalent intermediates have achieved widespread success. However, considerable limitations still exist for the linear reactions with electron-deficient alkenes, which are limited to 1,4-Michael acceptors. This report presents the first NHC-catalyzed asymmetric homoenolate addition of enals to 1,6-Michael acceptors. The strategy leads to the challenging nonspirocyclic 3,3-disubstituted oxindoles with two adjacent stereocenters, a quaternary and a trisubstituted one, in good yields and high stereoselectivities with a wide variety of substrates.

Keywords: N-heterocyclic carbene, homoenolate, 1,6-addition quaternary oxindole, asymmetric synthesis

Introduction

Since the turn of the millennium, organocatalysis emerged as an efficient tool for various synthetically important asymmetric bond formations,\textsuperscript{1,7} for instance, the asymmetric Michael additions.\textsuperscript{8–18} Although numerous strategies exist for asymmetric 1,4-conjugate additions of carbon nucleophiles, the analogous extension of this synthetic logic to the 1,6-addition remains underdeveloped because it is difficult to control the regio- and enantioselectivities.\textsuperscript{19–23} In 2007, Jørgensen and co-workers\textsuperscript{24} made a seminal contribution by developing an organocatalytic enantioselective 1,6-addition of enolates under phase-transfer catalysis. Later, a secondary amine catalyst was employed by them for the enantioselective 1,6-addition of dienolates.\textsuperscript{25} Further developments in this field have broadened the scope of carbon nucleophiles participation in these 1,6-addition reactions, with most studies focused on cycloaddition processes.\textsuperscript{26} Despite these achievements, asymmetric catalytic noncycloadditive reactions, generated through a homoenolate addition to 1,6-Michael acceptors, remain an unsolved problem (Scheme 1a). In view of the wide applications of homoenolate additions in organic and medicinal
chemistry, it is both important and urgent to expand these studies, as highly regio- and enantioselective 1,6-addition of homoenolates would facilitate the synthesis of related pharmaceutically active compounds and hopefully, open up new synthetic opportunities for asymmetric carbon–carbon bond formations.

One approach to efficiently generate homoenolate equivalent intermediates is using N-heterocyclic carbene (NHC)-catalyzed protocols,27–48 which have proven to be among the most powerful tools. In 2004, Glorius and Bode and their co-workers49,50 pioneered the NHC-catalyzed [3+2] cycloaddition of homoenolate equivalent intermediates and aldehydes. Since then, numerous NHC-catalyzed reactions, via homoenolate equivalent intermediates with activated double bonds have been developed by several groups.28,39 Surprisingly, although there are significant advances in cycloaddition reactions of homoenolate equivalent intermediates with Michael acceptors,51–62 the corresponding linear processes via homoenolate additions are largely unexplored (Scheme 1b). Currently, only two types of 1,4-Michael additions have been reported. In 2009, Nair et al.63 disclosed the first NHC-catalyzed 1,4-Michael addition of enals to nitroalkenes, whereas efficient enantioselective variants of this process were developed in 2013 by Rovis and Liu.64–66 Recently, Rovis and Flanigan67 reported another elegant example by employing alkyl pyridiniums as 1,4-Michael acceptors. To address the challenge of the efficient asymmetric 1,6-Michael addition of homoenolates, we sought to design a new broadly applicable methodological approach that provides access to carbon quaternary stereogenic centers with high regio- and stereoselectivities.

Several key challenges had to be tackled to accomplish the desired reaction (Scheme 1c): First, the more difficult one was suppression of the cycloaddition pathways. This is a severe problem, as it was evident from previous studies that the intermediate III could easily undergo cycloaddition processes, including domino processes,56–59 [3+2] cycloadditions,51–53,60 and [3+4] cycloadditions.54,55,61,62 Second, the 1,6-Michael addition of homoenolate equivalent intermediates had to be realized. Because this process would become more difficult if sterically hindered, β, β-disubstituted enals or δ, δ-disubstituted 1,6-Michael acceptors were employed as reaction partners. Third, the competing a2-d3 umpolung pathway had to be suppressed, which led to undesired Stetter products.68,69 In view of these challenges, a research program to explore the 1,6-addition of homoenolate equivalent intermediates was carried out. Herein,

Scheme 1 | Motivation and synthetic strategy of N-heterocyclic carbene (NHC)-catalyzed 1,6-addition of homoenolate equivalent intermediates.

Scheme 2 | Optimization of the asymmetric 1,6-addition of isatin-derived enals. Top: Synthesis of nonspirocyclic quaternary oxindole. Bottom: Histogram showing the results. Yield of isolated product 3a after chromatography. The ee was determined by high-performance liquid chromatography (HPLC) analysis of the purified product on a chiral stationary phase.
we report a new homoenolate addition of enals to 1,6-Michael acceptors for the catalytic asymmetric synthesis of nonspirocyclic quaternary 3,3-disubstituted oxindoles (Scheme 1d).

3,3-Disubstituted oxindoles are present in a wide range of natural products, drugs, and other medicinally relevant products. Their synthesis has fascinated many research groups, and quite a number of catalytic asymmetric methods have been developed for their synthesis. Despite substantial advances, enantioselectively enriched nonspirocyclic 3,3-disubstituted oxindoles remain challenging to access.\textsuperscript{70-79} During our continuous efforts devoted to the development of NHC-catalyzed 1,6-adding,\textsuperscript{60} a model reaction of the \( p \)-quinone methide\textsuperscript{81-85} 1a as 1,6-Michael acceptor and the isatin-derived enal\textsuperscript{84-86} 2a was investigated under NHC catalysis (Scheme 2). We were pleased to find that the reaction catalyzed using precatalyst A, in the presence of \( N,N \)-disopropylethylamine (DIPEA) as the base, furnished the desired nonspirocyclic quaternary oxindole 3a in 45% yield with 3:1 diastereomeric ratio (dr) and 67% enantiomeric excess (ee). The screening of the NHC-catalyst precursors (B-E) showed that the L-pyroglutamic-acid-derived precatalyst E was the best choice because the reaction outcome was improved by 65% yield with 4:1 dr and 89% ee.

With the optimized conditions in hand, the scope of the reaction was studied (Figure 1). A series of \( p \)-quinone methide 1 bearing electron-donating or electron-withdrawing substituents (\( \text{Ar} = 4\)-MeC\( \text{H}_2\), 4-BrC\( \text{H}_2\), and 3,4-Me\( \text{OCH}_2\text{CH}_3\)) reacted smoothly and gave the desired products 3b-d in moderate to good yields with 80-89% ee and 4:1-20:1 dr values. Even the reactions of substrates with sterically hindered ortho/ortho-, para/ortho-, meta-disubstituted aromatic ring proceeded efficiently and led to the corresponding products 3e-i in 45-63% yields with good to excellent diastereoselectivities and high enantioselectivities. This was also true for the heterocyclic substituents (\( \text{Ar} = \text{furfuryl and thiophenyl} \)), giving rise to products 3j and k. Notably, the isopropyl and methyl \( R^1 \) substituents of the \( p \)-quinone methides were also tolerated without apparent change in the enantioselectivities, albeit in somewhat decreased yields (3l and m). The scope of the reaction with respect to the isatin-derived enals was also examined. Substituents at different positions (\( R^2 = 5\)-Me, 6-Cl, and 5,7-Me\( \text{O} \)) had limited effect on the yields and stereoselectivities. The isatin-derived enals 2 with varying nitrogen protecting groups were also suitable reaction partners for the 1,6-additions (3q-v).

Alternatively, we decided to investigate the corresponding homoenolate addition of cinnamaldehydes to isatin-derived 1,6-Michael acceptors as the substituent, since the configuration at the C3 position of oxindoles has an important influence on biological activity. After optimizing the reaction conditions (see Supporting Information S17 and Table S1), we have successfully established the NHC-catalyzed 1,6-addition of cinnamaldehydes using 3-methyl-4-nitro-5-isatylidenyl-isoxazoles as 1,6-Michael acceptors and triazolium salt F as the precatalyst (Figure 2). A variety of cinnamaldehydes all reacted smoothly and provided the desired nonspirocyclic quaternary 3,3-disubstituted oxindoles 6a-f in good yields with uniformly high stereoselectivities.

The absolute configuration of the product 6a was determined by the X-ray structure analysis (see Figure 3). The reaction of the isatin-derivative enals, using \( p \)-quinone methides as 1,6-Michael acceptors, and \( N \),\( N \)-disopropylethylamine (DIPEA) as the base, furnished the desired nonspirocyclic quaternary 3,3-disubstituted oxindoles 3a-i, giving high diastereoselectivities, albeit in somewhat decreased yields (3j and m). The scope of the reaction with respect to the isatin-derived enals was also examined. Substituents at different positions (\( R^2 = 5\)-Me, 6-Cl, and 5,7-Me\( \text{O} \)) had limited effect on the yields and stereoselectivities. The isatin-derived enals 2 with varying nitrogen protecting groups were also suitable reaction partners for the 1,6-additions (3q-v).

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Figure 2 | Asymmetric 1,6-addition of cinnamaldehydes. Note: Synthesis of nonspirocyclic quaternary 3,3-disubstituted oxindoles by asymmetric 1,6-addition of cinnamaldehydes, using 3-methyl-4-nitro-5-isatylidenyl-isoxazoles as 1,6-Michael acceptors. Yields of isolated products after chromatography are presented. The ee was determined by HPLC analysis of the purified product on a chiral stationary phase.

Supporting Information, and the configurations of all other products were assigned accordingly.

Conclusion

In conclusion, we have developed first asymmetric linear reactions of homoenoate equivalent intermediates and 1,6-Michael acceptors using NHC catalysis. This protocol enables the efficient assembly of nonspirocyclic quaternary 3,3-disubstituted oxindoles in good yields with good to high stereoselectivities. In view of the promising properties of quaternary 3,3-disubstituted oxindoles, we anticipate that the presented catalytic stereoselective strategy will facilitate applications in the pharmaceutical and NHC-catalysis arenas.

Supporting Information

Supporting information is available.

Conflicts of Interest

The authors declare no competing interests.

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