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Oxidative N-Heterocyclic Carbene Catalyzed Diastereoselective Annulation of Simple Aldehydes and 5-Alkenyl Thiazolones: Facile Asymmetric Synthesis of Chiral Thiazo Pyrones†

Li Lin,‡a Yuhong Yang,‡a Mei Wang,‡a Luhao Lai,a Yarong Guoa and Rui Wangab,*

A highly diastereoselective annulation of simple aldehydes and 5-alkenyl thiazolones, via oxidative NHC catalysis has been developed. This strategy provides facile access to a diverse library of functionalized chiral thiazo pyrones. Aerobic oxygen can also be applied as a secondary oxidant to avoid the use of stoichiometric organic or inorganic oxidants.

N-Heterocyclic Carbene (NHC) catalysis has been brought forward and developed since middle of 20th century. However, asymmetric NHC catalysis has only gained popularity over the last decade resulting in further development of this research area. Beside the benzoin condensation and the Stetter reaction, oxidative NHC catalysis via the Breslow intermediate is the most widely applied model due to its broad applicability allowing for diverse transformations. The Breslow intermediate can be converted to the related positively-charged NHC intermediate (acyl azolium) via a redox process involving an α-ring-fused or α-halo aldehydes enals, and alkyals. Phenol esters, ketones, and acids as well as acyl fluorides can also be transformed to the acyl azolium intermediate. Aside from these methods, it is preferable to generate the positively-charged NHC intermediate directly from an unactivated aldehyde via an oxidative process with external oxidants. Stoichiometric or excess quantities of various organic or inorganic oxidants are generally explored. However, molecular oxygen has been rarely employed as an electron-transferring oxidant in asymmetric oxidative NHC catalysis.

The generation of the key acyl azolium intermediate from simple aliphatic aldehydes is highly desirable. Recently, the groups of Rovis and Chi separetely disclosed the asymmetric annulation of aliphatic aldehydes with simple α,β-unsaturated ketimines and ketones. As the commonly used 3,3',5,5'-tetrabutyl diphenoyl quinone (O-1) did not work in Rovis’ work, they exploited riboflavin tetra acetate (O-2) and phenazine instead. However, Chi et al. achieved their annulation of aliphatic aldehydes with simple chalcones when using O-1 as the oxidant. Although they report the use of catalytic quantities of O-1 in combination of MnO2 can afford similar result a highly excess amount of MnO2 was essential. Besides, the electrophile in reported works is limited to simple ketimines and chalcones. Asymmetric transformations of simple aliphatic aldehyde with other electrophiles rather than ketimines and chalcones are unknown. Protocols affording more complex structural motifs are highly desired. Thiazoles skeletons are found in many drug as well as bioactive compounds. In order to further exploit the bioactivities of such compounds, the development of new methodologies towards the synthesis of such scaffolds has always been an attractive field. The most attractive way to make highly functionalized chiral thiazo pyrones is via an asymmetric annulation of 5-alkenyl thiazolones with the requisite aldehyde, via an oxidative NHC protocol. Herein, we report the highly stereoselective annulation of aliphatic aldehydes with 5-alkenyl thiazolone via oxidative NHC catalysis. A series of chiral thiazo pyrones were obtained. Most noteworthy, in presence of aerobic oxygen, excellent stereoselectivity and moderate yield can also be achieved using the oxidant quinone O-1 in catalytic amount.

In our initial studies, 5-alkenyl thiazolone 1a and butyaldehyde 2a were used in the model reaction to optimize the reaction conditions. Stoichiometric O-1 was exploited to optimize the reaction conditions, involving solvent and base. Detailed optimization studies are shown in ESI (†). Note worthy, when using Et3N as the base and catalyzed by NHC-1, the highest yield (85%) of 3a was obtained, along with excellent diastereoselectivity (>20:1) and high ee of 92% (Table 1, entry 1). The ee value was increased to 95% when using NaOAc, and excellent d.r. (>20:1) also resulted (Table 1, entry 2). Thus, NaOAc was realized as the optimal base in this system, and used in the following studies. Variety of NHC pre-catalysts (NHC1–8) was also examined (For details see ESI†). The reactivity was greatly affected by the aryl substituents in the carbene ring. Interestingly, the two enantiomers of 3a and 3a’ were respectively obtained, while using NHC-2 and its opposite enantiomer NHC-5 (Table 1, entry 3 and 4). The absolute configurations of (R)3a and (S, S)-3a’ were confirmed via X-ray crystallography (Scheme 1) (†), which clearly indicated that the reaction give the chiral thiazo pyrone in cis-conformation. Therefore, in order to get the chiral thiazo pyrones in the desired high yield with excellent stereoselectivity, pre-catalyst NHC-2 and stoichiometric amount of O-1 were explored in the following studies.
Table 1. Representative screening studies on base and NHC pre-catalyst.[a]

<table>
<thead>
<tr>
<th>entry</th>
<th>pre-catalyst</th>
<th>base</th>
<th>yield%[b]</th>
<th>ee% [c]</th>
<th>d.r. [c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NHC-1</td>
<td>Et$_3$N</td>
<td>85</td>
<td>92</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>2</td>
<td>NHC-1</td>
<td>NaOAc</td>
<td>74</td>
<td>95</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>3</td>
<td>NHC-2</td>
<td>NaOAc</td>
<td>80</td>
<td>&gt;99</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>4</td>
<td>NHC-5</td>
<td>NaOAc</td>
<td>82</td>
<td>&gt;99[^d]</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>

[a] In freshly distilled THF, all the reactions were carried out with 1a (0.2 mmol), 2a (0.4 mmol), Base (0.4 mmol), O-1 (0.2 mmol), and NHC (0.02 mmol) at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis, and for details see ESI. [d] ee refers to 3a', enantiomer of 3a.

Scheme 1. X-ray structure of 3a and 3a'.

Under the optimal conditions, the reaction scope was investigated with a variety of 5-alkenyl thiazolones with simple aliphatic aldehydes. As shown in Scheme 2, both electron-deficient and electron-rich aryl substitutes of 5-alkenyl thiazolones were well tolerated in the asymmetric annulation. The desired chiral thiazolopyrones were afforded in moderate to good yields with excellent enantioselectivities (>99%) and diastereoselectivities being observed. Different substituents at the phenyl ring of the 5-alkenyl in compound 1 exerted a limited influence during the annulation (3b-3l). The decreased diastereoselectivity observed in the case of 3j (d.r. 10:1), may be due to the strong electron-withdrawing effect of the nitrile group. The hindrance of the o-MeO substituent may lead to the decreasing of the d.r. of 3l to 10:1. The chiral thiazolopyrone containing either a thieryl (3m) or a furyl (3n) motif was also successfully afforded in good yield with excellent ee (>99%) and diastereoselectivity (d.r. >20:1). In addition, other simple aliphatic aldehydes as well as 5-alkenyl thiazolone were also tolerated. The reaction of 1e with either propanal or heptanal proceeded successfully to afford the annihilation product 3o or 3p in good yields, and with excellent ee and d.r. values. While using isovaleraldehyde, excellent stereoselectivity of 3q was also observed. In contrast with Schießl’s work,[16] the substrate in the 2-aryl group of thiazolone did not affect the reactivity or the stereoselectivity of the annulation. Product 3r was obtained in good yield with 99% ee and high d.r. of 11:1. This result indicated that the present protocol could lead to more diverse chiral thiazolopyrones, which can be utilized in medicinal chemistry.

Scheme 2. Diastereoselective [4+2] annulation catalyzed by NHC-2. See the Supporting Information for details. All the reactions were carried out in THF at room temperature for the cited hours, using different 5-alkenyl thiazolone (0.2 mmol), simple aldehyde (0.4 mmol), NaOAc (0.2 mmol), O-1 (0.2 mmol), and NHC-2 (0.02 mmol). The yield refers to isolated yield. The ee value and diastereomeric ratio (d.r.) were determined by HPLC analysis, and for details see ESI.

As commonly known, 3,3',5,5'-([Bu]$_2$)-biphenyl-4,4'-dil (O-1$^b$) is the reduced form of the oxidant O-1. The phenol O-1$^b$ can also be oxidized to O-1 by molecular oxygen, during which would generate one molecule of H$_2$O.[17] However, no report exploiting catalytic amount of O-1 in combination of oxygen has been disclosed. Therefore, we attempted to develop an oxidative NHC catalysis in catalytic use of O-1. According to the initial studies, the product was obtained in the highest yield while the reaction was catalyzed by NHC-1 and using Et$_3$N as the base (Table 1, entry 1). NHC-1/Et$_3$N catalytic system was then exploited to further screen the required amount of O-1 in presence of molecular oxygen (Table 2).
The desired products were obtained in moderate yield while using catalytic amount of O-1.\[a\] Based on the recovered starting material (entry 1). Surprisingly, no decrease in either enantioselectivity or diastereoselectivity was observed while reducing the amount of O-1 from 100 mol% to 5 mol% (Table 2, entry 2-5). But the conversion was affected catalytically using O-1. Excitingly, the quinone O-1 can even be reduced to 2 mol% without losing stereoselectivity (Table 2, entry 6). When using 2 mol% of O-1, chiral thiazolo pyrones 3d and 3f were also obtained in moderate yield with excellent ee (>99%) and high d.r. (14:1 and >20:1, respectively) (Table 2, entry 7-8). But corresponding 1d and 1f can be recovered in 30% to 40%. The exact reason for the starting material being not fully converted remains unknown. The in-situ generation of H\(_2\)O might be a possible influence on the reaction outcome. Although the desired products were obtained in moderate yield while using catalytic amount of O-1, this work indicates the oxidant O-1 in combination of molecular oxygen can be an efficient and green oxidation system in oxidative NHC catalysis.

Without using O-1, the model reaction gave the thiazolo pyrone 3i in poor yield with complex by-products (Table 2, entry 1). Surprisingly, no decrease in either enantioselectivity or diastereoselectivity was observed while reducing the amount of O-1 from 100 mol% to 5 mol% (Table 2, entry 2-5). But the conversion was affected catalytically using O-1. Excitingly, the quinone O-1 can even be reduced to 2 mol% without losing stereoselectivity (Table 2, entry 6). When using 2 mol% of O-1, chiral thiazolo pyrones 3d and 3f were also obtained in moderate yield with excellent ee (>99%) and high d.r. (14:1 and >20:1, respectively) (Table 2, entry 7-8). But corresponding 1d and 1f can be recovered in 30% to 40%. The exact reason for the starting material being not fully converted remains unknown. The in-situ generation of H\(_2\)O might be a possible influence on the reaction outcome. Although the desired products were obtained in moderate yield while using catalytic amount of O-1, this work indicates the oxidant O-1 in combination of molecular oxygen can be an efficient and green oxidation system in oxidative NHC catalysis.

A catalytic model is proposed and shown in Scheme 3. Firstly, the in-situ generated free carbene catalyst NHC can react with the aldehyde 2a to form the Breslow intermediate I. The acyl azolium II is then generated via oxidizing Breslow intermediate I by O-1. The enolate form of acyl azolium (II') which is the real active species, can be easily formed in the presence of base. Subsequently, enolate intermediate II' in combination of the alkenyl thiazoline will undergo the [4+2]-annulation or Michael addition to construct the new six-member ring intermediates (III and III', respectively). To simplify the figure, a gray panel was used to block the frameworks behind the surface. The product as well as the free carbene NHC can be afforded from the zwiterion intermediate III or III'. If in the presence of molecular oxygen, the quinone O-1 can be re-generated via oxidation of O-1, during which one molecular of H\(_2\)O is generated. However, the in-situ generated H\(_2\)O may affect the formation of the enolate intermediate II' as well as the annulation process. Therefore, when using catalytic amount of O-1, the in-situ generated H\(_2\)O may caused the lower yield.

In conclusion, we have developed an oxidative NHC-catalyzed annulation of 5-alkenyl thiazolines with simple aliphatic aldehydes under mild conditions. A broad substrate scope was tolerated in the present method. Thus, a series of structural diverse chiral thiazolo pyrones were obtained in good yield with excellent enantioselectivity as well as diastereoselectivity. It was also found the common oxidant quinone O-1 can be used in catalytic amount and be re-generated in the presence of molecular oxygen, which indicates this method is a more efficient and greener oxidation system for oxidative NHC catalysis.

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Notes and references
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\[c\] Electronic Supplementary Information (ESI) available. CCDC 1040952 (3a) and CCDC 1040953 (3a') contain the supplementary crystallographic data for this paper. For ESI and crystallographic data in CIF or other electronic format see See DOI: 10.1039/c000000x/
\[d\] These two authors contributed equally.
\[†\] Although Rovis group (ref. 14a) reported a 74% yield obtained in the model reaction when using catalytic riboflavin tetra acetate (Riboflavin-Ac, or O-2 in Scheme 2) under “rigorous exclusion of oxygen” condition, it was confused to find that the reaction resulted in only low yield (<20%) under oxygen. However, they did not give a clear and reasonable discussion.
