Highly Enantioselective Catalytic Addition of Grignard Reagents to N-Heterocyclic Acceptors

Yafei Guo and Syuzanna R. Harutyunyan*

Abstract: General methods to prepare chiral N-heterocyclic molecular scaffolds are greatly sought after because of their significance in medicinal chemistry. Described here is the first general catalytic methodology to access a wide variety of chiral 2- and 4-substituted tetrahydro-quinolones, dihydro-4-pyridones, and piperidones with excellent yields and enantioselectivities, utilizing a single catalyst system.

Optically active piperidine and tetrahydroquinoline derivatives are ubiquitous structural motifs in alkaloid-based natural products, and bioactive and pharmaceutical compounds. Some examples to be highlighted include Torcetrapib, a drug used to treat elevated cholesterol levels, the antibiotic Helquinolone, as well as various alkaloids such as the Angustureina, Conine, Myrrine, Solenopsin series and Indolizidine (Scheme 1A).[1] Accordingly, chiral piperidine and tetrahydroquinoline derivatives represent important synthetic targets. General asymmetric synthetic routes for their synthesis rely on several strategic approaches (Scheme 1B).

Other potential alternative N-heterocyclic precursors for the synthesis of chiral piperidine and tetrahydroquinoline derivatives include piperidones, dihydropyridones, and quinolones, which in addition are often found as part of more complex biologically active compounds.[4] However, catalytic enantioselective methodologies for conjugate additions to, for example quinolone, pyridone, dihydropyridone, and acylpyridinium salts, would constitute more attractive routes. Several such methods for additions of organometallics to 4-quinolones and dihydropyridone have been developed to date, with the most successful examples focusing on arylation.[6] In contrast, for asymmetric alkylations there are only a few reports which make use of dihydropyridone[6f,g] and an acylpyridinium salt.[1a,7,8b] These alkylaton methods suffer from limited product scope with either low yields or moderate enantioselectivities. Furthermore, catalytic asymmetric alkylation of 4-quinolones and catalytic asymmetric conjugate additions, in general, to 2-quinolones as well as 4-pyridone[6h] are unknown. In pursuit

Scheme 1. A) Examples of pharmaceuticals and natural products featuring chiral N-heterocyclic core. B) State of the art. C) This work.
of a catalytic asymmetric approach to a wide variety of chiral N-heterocyclic compounds we were interested in developing a single catalytic system capable of harnessing the reactivity of various N-heterocyclic acceptors.

Herein, we describe the first general protocol for catalytic asymmetric addition of various Grignard reagents to a wide variety of N-heterocyclic acceptors with excellent yields and enantioselectivities (Scheme 1C), and it requires a single catalytic system based on a copper salt and chiral diphosphine ligand.

Our initial studies focused on the development of an efficient catalytic methodology for the alkylation of 4-quinolones (Table 1). To compensate for the relatively low reactivity of the 4-quinolone acceptor, we decided to take advantage of the high reactivity of Grignard reagents. For the screening of catalytic systems and reaction conditions we chose the addition of EtMgBr to the carboxybenzyl-protected (Cbz) 4-quinolone 1a as a model reaction. Addition of EtMgBr in the absence of any catalyst did not provide substrate conversion, even at room temperature (entry 1). First we set out to identify promising chiral catalysts, using 5 mol% of CuBr-SMe₂ and 6 mol% of various chiral ligands.

Table 1: Optimization of reaction conditions for the addition of EtMgBr to N-Cbz-4-quinolone (1a).[6]

<table>
<thead>
<tr>
<th>Entry</th>
<th>T [°C]</th>
<th>t [h]</th>
<th>Ligand</th>
<th>Yield [%][b]</th>
<th>ee [%][c]</th>
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<tbody>
<tr>
<td>1[6]</td>
<td>RT</td>
<td>-</td>
<td></td>
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<td>0</td>
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<tr>
<td>2</td>
<td>-78</td>
<td>12</td>
<td>L1</td>
<td>99</td>
<td>99</td>
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<td>-20</td>
<td>2</td>
<td>L1</td>
<td>99</td>
<td>99</td>
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<tr>
<td>4</td>
<td>0</td>
<td>2</td>
<td>L1</td>
<td>99</td>
<td>98</td>
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<tr>
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<td>0.5</td>
<td>1</td>
<td>L1</td>
<td>98</td>
<td>98</td>
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<tr>
<td>6</td>
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<td>21</td>
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</tr>
<tr>
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<td>RT</td>
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<td>L3</td>
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<td>32</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>RT</td>
<td>0.5</td>
<td>L6</td>
<td>71</td>
<td>0</td>
</tr>
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</table>

[a] Reaction conditions: N-Cbz-4-quinolone 1a (0.2 mmol), EtMgBr (2.0 equiv), L (6 mol%), and CuBr-SMe₂ (5 mol%) in CH₂Cl₂ (2 mL).
[b] Yields are those for the isolated products. [c] The enantiomeric excess was determined by HPLC on a chiral stationary phase. [d] Reaction without CuBr-SMe₂ and ligand.
The protocol could also enable addition reactions to N-Cbz-4-pyridone (3; Scheme 3). This substrate is more challenging for applications in catalysis as its aromatic character reduces the reactivity towards nucleophilic additions. As a result, pyridones have been hardly explored in asymmetric catalysis, even though there is major potential in the application of these substrates in chemical synthesis: after the initial conjugate addition reaction the resulting chiral N-heterocyclic product, with remaining Michael acceptor functionality, can subsequently undergo further stereoselective functionalizations to provide 2,6-substituted chiral pyridines, which can be useful for natural product synthesis. We initially evaluated the reactivity of 3 towards nucleophilic addition of EtMgBr using the reaction conditions optimized for N-Cbz-4-quinolones (Table 1, entry 2). Unfortunately the corresponding addition product 4a was not obtained, but instead the side products derived from the addition of EtMgBr to the carboxybenzyl moiety were found. To steer the chemoselectivity of the reaction towards 4a, we decided to introduce Lewis acids. With BF$_3$·OEt$_2$ as the Lewis acid the best possible results, with 95% yield and more than 99% enantiomeric purity, were obtained (Scheme 3). With these reaction conditions we assessed the scope with respect to the organomagnesium reagents for this reaction system. A number of chiral 2-substituted 2,3-dihydro-4-pyridone products derived from the addition of linear, β-, and γ-branched Grignard reagents were synthesized with high yields. In all cases excellent enantioselectivities were observed as well (ee values 94 to >99%).

Although asymmetric conjugate addition of aryloboronic acid, and aryl and dialkylzinc nucleophiles to N-substituted-2-quinolones has been well explored in recent years, we were interested in investigating the behavior of our catalytic system when applied to these substrates. Given their substantially higher reactivity than 3 we anticipated that Lewis acids would not be needed and that low temperatures would most likely be required to avoid noncatalyzed addition of Grignard reagents. Indeed, quick screening of several Grignard reagents, namely MeMgBr, EtMgBr, and nPrMgBr supported this notion and the corresponding chiral 2-substituted 4-piperidones (6a–c) were obtained with excellent yields and enantiomeric excesses above 90% (Scheme 4).

Our next quest was to access chiral products derived from additions to N-substituted-2-quinolones, which are formally cyclic α,β-conjugated amides and are expected to be less reactive than 4-quinolones (Scheme 5). We were pleased to find that when using 2-quinolones with an OMe protecting group at the N atom, the corresponding deprotected products 8a–h were obtained with excellent enantiomeric excess and chemical yields. However, to reach full conversion and high...
yields it is necessary to use a Lewis acid, with TMSBr performing best. Importantly, the methoxy substituent at the N atom is removed upon reaction work up. Using this reaction protocol we obtained a variety of products using various Grignard reagents as well as substrates with different substituents in the aromatic ring. It is noteworthy that this catalytic system tolerates 2-quinolone substrates with various protecting groups, such as Me, Bn, and allyl on N. The products 8i-k, derived from conjugate addition of EtMgBr to these substrates, were obtained with enantiomeric purities above 93 % and yields above 72 %.

Finally, to demonstrate the potential applications of our reaction protocol, we carried out a gram-scale reaction as well as several additional transformations, all depicted in Scheme 6.

In summary, we have developed the first general protocol for the alkylation of various classes of N-heterocyclic electrophiles with organomagnesium reagents, utilizing one catalytic system based on a Cu(I) complex with (R,R)-Ph-BPE. Alkylation of 2-quinolones, 4-quinolones, and 4-pyridones provides easy access to various derivatives of chiral 2- and 4-substituted tetrahydroquinolones and dihydro-4-pyridones in excellent yields and enantioselectivities. Significantly, addition reactions to N-substituted-4-quinolones can be carried out at room temperature, while consecutive alkylation of pyridone and the resulting 2,3-dihydro-4-pyridones allows convenient catalytic access to 2,6-substituted diastereomerically and enantiomerically pure piperidones. We anticipate that this methodology will be a valuable synthetic tool and find practical application in the synthesis of complex building blocks and natural and pharmaceutical compounds.

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[8] Pyridones have been explored in addition reactions with various organometallics only for non-asymmetric reactions (see the references below). In ref. [b] however one example of catalytic asymmetric addition was reported for the addition of Et₃Zn to 4-pyridone, furnishing the final product with 82% ee. a) F. Guo, R. C. Dhakal, R. K. Dieter, J. Org. Chem. 2013, 78, 8451–8464; b) R. K. Dieter, F. Guo, J. Org. Chem. 2009, 74, 3843–3848.


[12] For the optimization data see the Supporting Information.


[14] CCDC 1942935 (2k) and 1942936 (8j) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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