Enantioselective copper-catalysed addition of organometallic reagents using phosphoramidite ligands
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Chapter 5
Catalytic enantioselective addition of organozinc reagents to $N$–acyloxyiminium ions

The first catalytic enantioselective addition of organozinc reagents to in situ generated $N$-acyloxyiminium ions, using copper/phosphoramidite catalysts, is described.
5.1 Introduction

The asymmetric nucleophilic addition to the C=N double bond is one of the most versatile synthetic tools for the formation of optically active α-chiral amines. In the previous chapter a survey of the most efficient catalytic enantioselective methods for the addition of organozinc reagents to imine derivatives was presented. Several highly efficient enantioselective catalyzed procedures have been developed for the addition to imines protected via N-arylation (1) or activated via N-sulphonylation (2), N-phosphonylation (3) or N-acylation (4), however, much less synthetic effort has been directed towards the use of N-oxides (5) (Scheme 5.1).

Scheme 5.1

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Addition of Organozinc Reagents to N-Acyloxyiminium Ions

8, which can be used as building blocks for alkaloid synthesis6 or as precursors of α-aminoaldehydes through the thiazol to formyl conversion.7

Scheme 5.2 Enantioselective alkylation of N-benzyl-α-(2-thiazolyl)nitrone 6.

Ukaji and coworkers8 reported the enantioselective synthesis of propargylic hydroxylamines 10 via addition of a zinc acetylide reagent to acyclic nitrones such as 8. A stoichiometric amount of a zinc salt of the t-butyl ester of (R,R)-tartrate 12 was used as the chiral source. Interestingly, the addition of 0.2 equiv of an additive similar to the product, e.g. 11, resulted in an increase in the enantioselectivity observed (Scheme 5.3). A catalytic version of this method was reported recently by the same group.9

Scheme 5.3 Enantioselective alkynylation of the acyclic nitrone 9.

Another example of the enantioselective addition of functionalized organometallic reagents, involving a stoichiometric amount of a chiral ligand, is the addition of Reformatsky-type reagents to 3,4-dihydroisoquinoline N-oxides 13-14 (Scheme 5.4).10
Scheme 5.4 Asymmetric addition of Reformatsky-type reagents to N-oxides.

The nucleophile, prepared in situ from Et₂Zn and an iodoacetic acid ester, adds to the N-oxide, in the presence of 1 equiv of a magnesium zinc salt of (R,R)-DIPT, to give the corresponding β-hydroxylamino esters with enantioselectivities of up to 86%.

The first catalytic enantioselective addition reaction of organozinc reagents to 3,4-dihydroisoquinoline N-oxides 13-15 was developed by Ukaji et al.¹¹ (Scheme 5.5).

Scheme 5.5 Catalytic enantioselective addition of R₂Zn to N-oxides.

In this procedure 0.2 equiv of a magnesium zinc salt derived from an ester of (R,R)-tartrate was used to catalyze the reaction. The highest enantioselectivities were reached when the N-oxide was added slowly to a mixture of the catalyst prepared in situ and an excess of R₂Zn. Good isolated yields and enantioselectivities of up to 90% were obtained after 19 h at room temperature. The products of this reaction can be easily converted into the corresponding 1-alkyl-tetrahydroisoquinolines,¹¹d,e immediate precursors of biologically relevant alkaloids (Scheme 5.6).¹²
Addition of Organozinc Reagents to N-Acloyxyiminium Ions

Scheme 5.6 Some isoquinoline-based alkaloids.

Salsolidine, for example, is a potent inhibitor of human monoamine oxidases, while 1-methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ) is an endogenous substance which provides protection against the development of the Parkinson disease.

Prompted by the synthetic importance of 1-alkyl-tetrahydroisoquinolines, we decided to investigate the possibility of developing a new approach for their synthesis based on the use of chiral phosphoramidite ligands.

5.2 Results and discussion

5.2.1 From N-oxides to N-acyloyximinium ions

Initial attempts involved the addition of diethylzinc to 3,4-dihydroisoquinoline N-oxides in the presence of Cu(OTf)$_2$ and the chiral phosphoramidite (S,R,R)-L1. It was apparent from these preliminary studies that the combination of this catalyst system and N-oxide substrates was ineffective. The addition reaction afforded racemic 16 in all of the solvents used (Table 5.1, entries 1-4). The reason for this may be due to the ability of the oxygen atom of the starting material to coordinate strongly to metal centres, therefore displacing the chiral ligand from the copper complex.
Table 5.1 Addition of Et₂Zn to 3,4-dihydroisoquinoline N-oxide 13.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Additive</th>
<th>Ee(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Et₂O</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>TMSCl</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>ZnBr₂</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>MgBr₂</td>
<td>-</td>
</tr>
</tbody>
</table>

³¹P-NMR spectroscopic studies allowed for the formation of the precatalytic copper complex to be followed. When the phosphoramidite was mixed with Cu(OTf)₂ in toluene at room temperature, for 30 min, the signal at 146 ppm, corresponding to the free chiral ligand \((S,R,R)\)-L₁ (Figure 5.1a), was replaced by a new signal at 125 ppm (Figure 5.1b). The appearance of this new signal is attributed to the chiral copper complex formed in situ in which \((S,R,R)\)-L₁ coordinates the metal via the phosphorous atom. Addition of the N-oxide to a toluene solution resulted in a reappearance of the signal of the free phosphoramidite ligand, suggesting that the N-oxide had replaced the chiral ligand in the copper complex (Figure 5.1c). The poor resolution of the signals in Figure 5.1b and 5.1c is attributed to the presence of the paramagnetic Cu(II) species.

The use of additives such as TMSCl, ZnBr₂ and MgBr₂ that might compete for coordination to the oxygen atom of the substrate and therefore prevent the
Addition of Organozinc Reagents to N-Acloyoximinium Ions

displacement of the chiral ligand, did not lead to any improvement in enantiocontrol (Table 5.1, entries 5-7).

\[ \text{(S,R,R)-L1} \]
\[ \delta = 146 \text{ ppm} \]

\[ \text{Cu(OTf)2+ (S,R,R)-L1} \]
\[ \delta = 125 \text{ ppm} \]

\[ \text{N-oxide 13 addition} \]
\[ \delta = 146 \text{ ppm} \]

Figure 5.1 \(^{31}P\)-NMR spectra recorded in \(d^8\)-toluene at room temperature.

A second possibility to prevent the displacement of the chiral ligands from the precatalytic copper complex consists of blocking the coordination of the \(N\)-
oxide by covalent binding to an appropriate protecting group. It is known that the reaction of a nitrone such as 17 with an acyl halide leads to formation of an N-acyloxyiminium species 18. Such species can, under certain conditions, rearrange to form an amide or an imine or it can be trapped with a nucleophile at low temperatures to form 19. The latter can then be converted into the corresponding free amine 21 (Scheme 5.7). Moreover the formation of a N-acyloxyiminium species increases the reactivity of the C=N double bond toward nucleophilic attack.

![Scheme 5.7 Possible reactions of a N-acyloxyiminium species.](image)

5.2.2 Enantioselective addition to N-oxide via N-acyloxyiminium ions

The synthetic potential of the N-acyloxyiminium ions led us to explore the catalytic enantioselective addition of diethylzinc to species 22 obtained upon treatment of the N-oxide 13 with an acyl halide. A solution of the substrate 13 and benzoyl chloride in toluene was stirred for 30 min, at -78 °C to form the N-acyloxyiminium ion 22. To this solution, the freshly prepared copper complex, formed from Cu(OTf)2 and the chiral ligand (S,R,R)-L1 was added, followed by an excess of Et2Zn (Scheme 5.8). However the desired product 21 was isolated in racemic form for all of the phosphoramidite ligands tested.
Addition of Organozinc Reagents to N-Acyloxyiminium Ions

Scheme 5.8 Addition of Et₂Zn to 13 via the N-acyloxyiminium species 22.
A study of the solvent influence showed that the use of chlorinated solvents is essential to achieve enantiocontrol in the reaction (Table 5.2).

Table 5.2 Solvent dependence of the addition of Et₂Zn to 22.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>70</td>
<td>rac</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>65</td>
<td>rac</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Et₂O</td>
<td>66</td>
<td>rac</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>EtOAc</td>
<td>-</td>
<td>-</td>
<td>Starting material</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>45</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>CHCl₃</td>
<td>73</td>
<td>10</td>
<td>-65 °C</td>
</tr>
<tr>
<td>7</td>
<td>Cl(CH₂)₂Cl</td>
<td>56</td>
<td>12</td>
<td>-35 °C</td>
</tr>
</tbody>
</table>
With the chiral phosphoramidite \((S,R,R)\)-L1, product 23 was isolated in good yield albeit as a racemate, in toluene, THF and Et2O (Table 5.2, entries 1-3). The reaction did not proceed in EToAc (entry 4), while in chlorinated solvents modest to good yields of 23 were obtained and enantioselectivities of up to 37% were observed (entries 5-7). The temperature chosen to carry out the additions in CHCl3 and 1,2-dichloroethane was set according to the freezing point of the solvent. Because the highest enantioselectivity for 21 (37%) was reached in CH2Cl2, the following investigations were conducted in this solvent.

The use of a copper source other than Cu(OTf)2 did not lead to an improvement of the enantioselectivity observed for 23, albeit the use of Cu(acac)2 or Cu(OAc)2·H2O led to a better isolated yield of, respectively, 68% and 82% (Table 5.3, entries 4 and 5).

Table 5.3 Screening of copper salts in the Et2Zn addition to 20.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu salt</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)2</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>CuCl</td>
<td>43</td>
<td>rac</td>
</tr>
<tr>
<td>3</td>
<td>CuTC</td>
<td>39</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>Cu(acac)2</td>
<td>68</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)2·H2O</td>
<td>82</td>
<td>18</td>
</tr>
</tbody>
</table>

The influence of the counter ion of the acyloxyiminium ion was taken into consideration. Use of benzoyl bromide, instead of benzoyl chloride, to generate the N-acyloxyiminium species 24, resulted in a complete loss of enantiocontrol, albeit the final product was obtained in higher yield (75%).
**Table 5.4** Counter ion effect.

<table>
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<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>86</td>
<td>rac</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>75</td>
<td>rac</td>
</tr>
</tbody>
</table>

This effect can be rationalised in terms of the equilibrium depicted in Figure 5.2. A ¹H-NMR spectroscopic study was carried out to characterize the N-acyloxyiminium ion 18 generated in situ from the N-oxide 17 and acetyl chloride.¹¹d Acetyl chloride was chosen as the acylating agent, instead of benzoyl chloride, to avoid overlap of the signals in the spectra. After mixing 15 and acetyl chloride in CDCl₃, at -78 °C for 30 min, the ¹H-NMR spectrum showed two sets of signals corresponding to the iminium ion 18 and the α-chloroamine 25, derived from the nucleophilic attack of the chloride on 18. The integration of the NMR signals revealed a ratio 1:11 in favour of 25. When BBr₃ was added to the mixture to trap the chloride, the N-acyloxyiminium ion 26 was the only species present. Exclusive formation of the N-acyloxyiminium ion 18 was recorded using acetyl bromide as the acylating agent, also.¹¹d

![Equilibrium between the N-acyloxyiminium ion 18 and the α-chloroamine 25.](image_url)

**Figure 5.2** Equilibrium between the N-acyloxyiminium ion 18 and the α-chloroamine 25.¹¹d
By analogy, the existence of an equilibrium between the iminium ion and the α-haloamine upon acylation of the N-oxide 13 is possible (Figure 5.3). If the α-chloroamine 27 is formed preferentially when using benzoyl chloride, the reactive species 22 will probably be formed gradually in situ during the reaction. As the concentration of the reacting N-acyloxyiminium ion in solution is maintained at a constant, low, level, then the relative amount of the catalyst will be considerably higher than 5 mol%. Such an effect might have a positive influence on the enantiocontrol of the addition reaction. By contrast, the absence of the aforementioned equilibrium in the case of the bromide counter ion, might result in a considerable decrease in the enantioselectivity observed.

Figure 5.3 Equilibrium between the N-acyloxyiminium ion and the α-chloroamine formed from 13.

Having established the importance of the counter ion to the enantioselectivity of the reaction, the effect of a change in the nature of the acyl chloride was evaluated. Substitution of benzoyl chloride for an aliphatic acyl chloride resulted in a racemic product (Table 5.5, entries 2 and 3). Complete loss of enantioselectivity was observed using the 2-naphthoyl chloride, also (entry 4). All the other aromatic acyl chlorides tested, however, provided a modest enantioselectivity in the corresponding Et₂Zn addition product. The highest ee (50%) and the highest yield (91%) were achieved where 2,4,6-trimethylbenzoyl chloride was employed as the acylating agent (entry 6). A further improvement was not observed upon increasing of the steric interactions of the protecting group (entry 7). Substitution of the aromatic moiety of the acyl chloride with electron-donating groups afforded good yields of the desired product and a modest enantioselectivity of 46% (entry 8) for the 2,4-dimethoxybenzoyl chloride and 32% for the 2,6-dimethoxybenzoyl chloride (entry 9). When acyl chlorides bearing electron-withdrawing groups were employed, only addition products of the Et₂Zn to the acyl group were detected (entries 10 and 11). It is
possible that the higher efficiency of the aromatic acyl chlorides in inducing enantioselectivity is due to presence of $\pi,\pi$-interactions between the protecting group and the aromatic moiety of the tetrahydroisoquinoline, which can shield one side of the molecule from the nucleophilic attack.

**Table 5.5 Effect of protecting groups on the addition of Et$_2$Zn.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>23</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>29</td>
<td>70</td>
<td>rac</td>
</tr>
<tr>
<td>3</td>
<td>$t$-Bu</td>
<td>30</td>
<td>52</td>
<td>rac</td>
</tr>
<tr>
<td>4</td>
<td>2-naphthyl</td>
<td>31</td>
<td>53</td>
<td>rac</td>
</tr>
<tr>
<td>5</td>
<td>9-anthraceny</td>
<td>32</td>
<td>42</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>2,4,6-trimethylbenzoyl</td>
<td>33</td>
<td>91</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>2,4,6-triisopropylbenzoyl</td>
<td>34</td>
<td>66</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>2,4-dimethoxybenzoyl</td>
<td>35</td>
<td>73</td>
<td>46</td>
</tr>
<tr>
<td>9</td>
<td>2,6-dimethoxybenzoyl</td>
<td>36</td>
<td>63</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>3,5-dinitrobenzoyl</td>
<td>37</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>2,4-dinitrobenzoyl</td>
<td>38</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

2,4,6-Trimethylbenzoyl chloride, which gave the highest yield and enantioselectivity in the addition of Et$_2$Zn to the N-oxide 13, was used to generate the corresponding N-acyloxyiminium ion in the subsequent studies.

Several monodentate phosphoramidite ligands were tested in the reaction reported in Scheme 5.9. Variation of the amine moiety of ($S,R,R$)-L1 resulted in a dramatic decrease of the enantioselectivity observed for 33. A modest 39% ee was obtained using a combination of ($S,R,R$)-L1 and ($S$)-L4 in 1:1 ratio (Scheme 5.9a). The influence of 3,3'-substitution on the BINOL moiety of the ligand was studied also. A series of substituted ligands derived from ($R$)-L9 was employed in the addition reaction. The presence of substituents on the
BINOL moiety of the ligands (R)-L10-(R)-L13 resulted in an improvement of the enantioselectivity compared to the unsubstituted ligand (R)-L9.

Scheme 5.9 Monodentate phosphoramidite ligands discussed in the text and yields and ee’s obtained in the addition of Et₂Zn to 13.
Nearly racemic 33 was isolated using the chiral ligand (R)-L14 (Scheme 5.9b). Bidentate phosphoramidite and phosphine ligands were tested as well, however the product was obtained as a racemate in all cases (Scheme 5.10).

Scheme 5.10 Bidentate ligands.

In summary, the copper complex formed from Cu(OTf)₂ and the chiral phosphoramidite ligand (S,R,R)-L1 showed the highest efficiency in catalyzing the addition of Et₂Zn to the N-acyloxyiminium ion generated in situ from the N-oxide 13 and 2,4,6-trimethylbenzoyl chloride. The reaction is sensitive to any variation of the reaction conditions. Enantioselectivity is achieved only in chlorinated solvents. The difference in the results obtained in terms of isolated yield and enantioselectivity with different copper salts indicate that the copper counter ion plays a role also. Monodentate phosphoramidite ligands proved to be more efficient in inducing enantiocntrol in the reaction than bidentate ligands, however differences in the chirality and steric properties of the ligand result in a range of enantioselectivities between 2% and 52%. These observations are not surprising considering that the outcome of copper catalyzed conjugate additions is known to be strongly dependent on the salt, the solvent and the structure of the phosphoramidite ligand used (see Chapter 1). These factors have been shown to influence the structure and the aggregation level of the precatalyst system formed in solution. Much less is known about the catalyst in its active form, however if such an influence is transferred to the structure of the latter, the variation of copper salt, solvent and
ligand might account for the formation of different species, showing different reactivity and enantioselectivity.

At present, the tools available for the prediction of the optimal combination of copper salt and ligand are still limited. A thorough screening of the reaction conditions remains the most appropriate way to proceed. A detailed mechanistic study of the copper catalyzed conjugate addition of organozinc reagents is necessary to gain further insight in the effects observed upon variation in the reaction parameters.

5.2.3 Scope of organozinc reagents

The addition of other commercially available organozinc reagents to the N-acyloxyiminium ion, generated in situ from the N-oxide 13 and 2,4,6-trimethylbenzoyl chloride, was explored. The results are listed in Table 5.6. The addition of Me₂Zn afforded the methylated product 39 in good yield (80%) but with low enantioselectivity (entry 2). The high reactivity of i-Pr₂Zn resulted in the addition of the organometallic species to the acyl chloride, precluding formation of the desired product. n-Bu₂Zn afforded compound 41 with 55% ee, albeit in lower yield than employing Et₂Zn (entry 4).

Table 5.6 Enantioselective addition of organozinc reagents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>33</td>
<td>91</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>39</td>
<td>80</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>40</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>n-Bu</td>
<td>41</td>
<td>57</td>
<td>55</td>
</tr>
</tbody>
</table>

Me₃Al is a potential alternative to Me₂Zn for the introduction of a methyl group, however with this reagent a mixture of addition products derived from the
attack of the reactive Me₃Al to the acyloxy moiety and to the free N-oxide were obtained.

5.3 Conclusions

The first catalytic enantioselective addition of organozinc reagents to N-acyloxyiminium ions to synthesize chiral-substituted tetrahydroisoquinolines has been reported. The reactive species are generated in situ from the corresponding nitrone and an acyl chloride. Optimization of the reaction conditions in terms of acyl halide, copper source, chiral ligand, temperature and solvent provided enantioselectivities of up to 55% using a catalyst formed in situ from Cu(OTf)₂ and the phosphoramidite ligand (S,R,R)-L₁. The product of the reaction can be deprotected to the corresponding hydroxylamine and further reduced to the free amine.²

The reaction proved to be highly sensitive to variation of the reaction parameters. However, it was established that chlorinated solvents and low temperatures were essential to achieve enantioselectivity; in particular, the best results were obtained with CH₂Cl₂ at -78 °C. Acyl halides are excellent reagents for the in situ formation of the N-acyloxyiminium species. Other reagents such as Boc anhydride, triflic anhydride, chloroformates and sulfonyl chlorides did not react with the N-oxide ¹³ at low temperature. The nature of the halide plays an important role also (vide supra). When bromide was used as the counterion of the N-acyloxyiminium species only racemic products were obtained. Several copper salts and chiral ligands were examined and the combination of Cu(OTf)₂ and the phosphoramidite (S,R,R)-L₁ was found to be the most efficient, however further investigations, eventually based on the use of libraries of ligands may be necessary to find the optimal catalyst system.

Another possibility is to replace the diorganozinc reagents with a different organometallic species. The high reactivity of organomagnesium and organoaluminium compounds makes these systems unsuitable because of the formation of side products derived from the attack on the acyloxy moiety. Less reactive organozinc halides, however, would significantly broaden the scope of the reaction enabling the introduction of both alkyl and aryl groups. Furthermore, the use of Reformatsky-type reagents¹⁰ could open the way to the development of new catalytic enantioselective routes for the asymmetric synthesis of β-amino acids.
5.4 Experimental section

General Methods. For general information see Chapter 2.

3,4-Dihydroisoquinoline 2-oxide (13). 

Compound 13 was synthesized according to a literature procedure. $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ = 7.73 (s, 1H), 7.26-7.19 (m, 3H), 7.11-7.08 (m, 1H), 4.09 (t, $J$ = 7.7 Hz, 2H), 3.16 (t, $J$ = 7.7 Hz, 2H) ppm. HRMS calcd. for C$_9$H$_9$NO: 147.0684, found: 147.0681.

1-Ethyl-3,4-dihydroisoquinolin-2(1H)-ol (16). 

Cu(OTf)$_2$ (3.6 mg, 0.010 mmol) and ligand (S,R,R)-L1 (10.8 mg, 0.020 mmol) were dissolved in the solvent indicated (3 mL) and stirred for 30 min at r.t. The mixture was cooled to -20 °C and a solution of the substrate in the same solvent (0.25 mmol, 0.125 M) was added. A solution of a R$_2$Zn (1.25 mmol) in the solvent indicated was added dropwise and the reaction mixture was stirred for 16 h at -20 °C, then quenched with sat. aq. NH$_4$Cl (10 mL) and extracted with EtOAc (3x 5 mL). The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), filtered and concentrated. Purification by column chromatography (SiO$_2$; CH$_2$Cl$_2$/MeOH 15:1) afforded compound 16 as a colorless oil. HPLC on a Chiralcel OD-H column, 4.6 × 250 mm, 5 µm, (n-heptane/propan-2-ol = 99.5:0.5, flow = 0.5 mL/min): Rt = 22.6 min, Rt = 25.0 min. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 7.18-7.11 (m, 3H), 7.09-7.07 (m, 1H), 3.96 (t, $J$ = 5.3 Hz, 1H), 3.47-3.41 (m, 1H), 3.21-3.15 (m, 1H), 3.02-2.86 (m, 2H), 2.10-2.00 (m, 1H), 1.92-1.81 (m, 1H), 0.93 (t, $J$ = 7.4 Hz, 3H) ppm. $^{13}$C-NMR (50 MHz, CDCl$_3$) $\delta$ = 136.6, 133.8, 128.3, 126.9, 126.1, 126.0, 68.0, 51.8, 26.4, 9.8. MS-CI found for C$_{11}$H$_{15}$NO: 178 [M+H$^+$].

General procedure for the copper/phosphoramidite catalyzed addition of dialkylzinc reagents to N-acyloxyiminium ions.

Cu(OTf)$_2$ (3.6 mg, 0.010 mmol) and ligand (S,R,R)-L1 (10.8 mg, 0.020 mmol) were dissolved in anhydrous CH$_2$Cl$_2$ (3 mL) and stirred for 30 min at r.t. A solution of the acyl halide in anhydrous CH$_2$Cl$_2$ (0.25 mmol, 0.25 M) was added dropwise, at -78 °C to a solution of compound 13 in anhydrous CH$_2$Cl$_2$ (0.25 mmol, 0.25 M). The mixture was stirred for 30 min at -78 °C. To this mixture a
solution of a \( \text{R}_2\text{Zn} \) (1.25 mmol) in the solvent indicated was added dropwise and the reaction mixture was stirred for 16 h at -78 °C, then quenched with sat. aq. \( \text{NH}_4\text{Cl} \) (10 mL) and extracted with \( \text{CH}_2\text{Cl}_2 \) (3x 5 mL). The combined organic extracts were washed with brine, dried (\( \text{Na}_2\text{SO}_4 \)), filtered and concentrated. The crude product was purified by flash chromatography.

1-Ethyl-3,4-dihydroisoquinolin-2(1\(H\))-yl benzoate (23).

Purification by column chromatography (SiO\(_2\); EtOAc/pentane 4:96) afforded compound 23 as a colorless oil (Rf = 0.6). HPLC on a Chiralpak AD column, 4.6 × 250 mm, 10 µm, (\(n\)-heptane/propan-2-ol = 97:3, flow = 1.0 mL/min): Rt = 7.2 min (major), Rt = 12.3 min (minor). 37% ee. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.95 \text{ (d, } J = 7.6 \text{ Hz, 2H, } 7.53 \text{ (t, } J = 7.3 \text{ Hz, 1H, } 7.40 \text{ (t, } J = 7.7 \text{ Hz, 2H, } 7.21-7.14 \text{ (m, 4H), 4.30 (t, } J = 5.9 \text{ Hz, 1H), 3.71-3.65 (m, 1H), 3.54-3.47 (m, 1H), 3.04 (t, } J = 6.1 \text{ Hz, 2H), 2.00-1.88 (m, 2H), 1.09 (t, } J = 7.3 \text{ Hz, 3H) ppm.} \)\(^{13}\)C-NMR (50 MHz, CDCl\(_3\)) \(\delta = 164.9, 136.2, 133.4, 123.9, 129.4, 129.3, 128.5, 128.3, 12.6. 8, 126.3, 126.1, 66.4, 49.6, 27.5, 25.5, 10.3 ppm. MS-CI calcd. for C\(_{18}\)H\(_{19}\)NO\(_2\): 282 [M+H]+. HRMS calcd. for C\(_{16}\)H\(_{14}\)NO\(_2\) [M-Et]: 252.1025, found 252.1032.

1-Ethyl-3,4-dihydroisoquinolin-2(1\(H\))-yl acetate (29).

Purification by column chromatography (SiO\(_2\); EtOAc/pentane 5:95) afforded compound 29 as a colorless oil (Rf = 0.5). HPLC on a Chiralcel OB-H column, 4.6 × 250 mm, 5 µm, (\(n\)-heptane/propan-2-ol = 95:5, flow = 0.5 mL/min): Rt = 13.1 min, Rt = 15.4 min. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.20-7.09 \text{ (m, 4H), 4.10 (t, } J = 5.8 \text{ Hz, 1H), 3.38-3.32 (m, 1H), 3.28-3.22 (m, 1H), 2.94 (t, } J = 5.8 \text{ Hz, 2H), 2.03 (s, 3H), 1.89-1.81 (m, 2H), 1.03 (t, } J = 7.4 \text{ Hz, 3H) ppm.} \)\(^{13}\)C-NMR (50 MHz, CDCl\(_3\)) \(\delta = 169.6, 136.1, 133.3, 128.4, 126.8, 126.3, 126.0, 66.2, 49.3, 27.5, 25.3, 19.7, 10.3 ppm. HRMS calcd. for C\(_{13}\)H\(_{17}\)NO\(_2\): 219.1259, found 219.1258.

1-Ethyl-3,4-dihydroisoquinolin-2(1\(H\))-yl pivalate (30).

Purification by column chromatography (SiO\(_2\); EtOAc/pentane 5:95) afforded compound 30 as a colorless oil (Rf = 0.6). HPLC on a Chiralpak AD column, 4.6 × 250 mm, 10 µm, (\(n\)-heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): Rt = 4.7 min, Rt = 5.5 min. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta = 191\)
7.17-7.08 (m, 4H), 4.10 (t, J = 5.9 Hz, 1H), 3.56-3.49 (m, 1H), 3.35-3.29 (m, 1H), 2.96-2.92 (m, 2H), 1.89-1.81 (m, 2H), 1.17 (s, 9H), 1.03 (t, J = 7.4 Hz, 3H) ppm. \(^{13}\text{C-NMR}\) (50 MHz, CDCl\(_3\)) \(\delta = 176.2, 136.3, 133.4, 128.4, 126.7, 126.2, 126.0, 109.9, 66.1, 49.3, 38.6, 27.1, 25.5, 10.2\) ppm. HRMS calcd. for C\(_{14}\)H\(_{18}\)NO\(_2\): 232.1337, found 232.1346.

1-Ethyl-3,4-dihydroisoquinolin-2(1\(H\))-yl 2-naphthoate (31).

Purification by column chromatography (SiO\(_2\); EtOAc/pentane 5:95) afforded compound 31 as a colorless oil (R\(_f\) = 0.6). HPLC on a Chiralpak AD column, 4.6 \(\times\) 250 mm, 10 \(\mu\)m, (n-heptane/propan-2-ol = 98:2, flow = 1.0 mL/min): Rt = 14.3 min, Rt = 31.5 min. \(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)) \(\delta = 8.52\) (s, 1H), 7.98-7.91 (m, 2H), 7.87-7.83 (m, 2H), 7.60-7.51 (m, 2H), 7.23-7.16 (m, 2H), 4.36 (t, J = 5.8 Hz, 1H), 3.74-3.70 (m, 1H), 3.58-3.52 (m, 1H), 3.08 (t, J = 6.1 Hz, 2H), 2.02-1.91 (m, 2H), 1.11 (t, J = 7.4 Hz, 3H) ppm. \(^{13}\text{C-NMR}\) (50 MHz, CDCl\(_3\)) \(\delta = 165.1, 136.3, 135.4, 133.5, 132.3, 130.8, 129.3, 128.5, 128.2, 128.1, 127.7, 126.8, 126.6, 126.3, 126.0, 125.0, 66.5, 49.8, 27.5, 25.7, 10.4\) ppm. HRMS calcd. for C\(_{20}\)H\(_{16}\)NO\(_2\): 302.1181, found 302.1190.

1-Ethyl-3,4-dihydroisoquinolin-2(1\(H\))-yl anthracene-9-carboxylate (32).

Purification by column chromatography (SiO\(_2\); EtOAc/pentane 5:95) afforded compound 32 as a yellow solid (R\(_f\) = 0.5). Mp. = 92.1-92.5 °C. HPLC on a Chiralpak AD column, 4.6 \(\times\) 250 mm, 10 \(\mu\)m, (n-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 11.5 min (major), Rt = 31.3 min (minor). 23% ee. \([\alpha]_D^\circ = +7.5\) (c 0.97, CHCl\(_3\)). \(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)) \(\delta = 8.48\) (s, 1H), 8.04 (d, J = 8.5 Hz, 2H), 7.98 (d, J = 8.3 Hz, 2H), 7.52-7.44 (m, 4H), 7.18-7.12 (m, 3H), 7.09-7.07 (m, 1H), 4.42 (t, J = 5.8 Hz, 1H), 3.96-3.89 (m, 1H), 3.74-3.68 (m, 1H), 3.06 (t, J = 6.2 Hz, 2H), 2.05-1.95 (m, 2H), 1.22 (t, J = 7.3 Hz, 3H) ppm. \(^{13}\text{C-NMR}\) (50 MHz, CDCl\(_3\)) \(\delta = 168.2, 136.0, 133.2, 130.8, 130.6, 129.3, 128.6, 128.5, 127.7, 126.9, 126.8, 126.6, 126.4, 126.1, 125.6, 125.4, 124.6, 124.5, 66.6, 49.7, 27.7, 25.5, 10.4\) ppm. HRMS calcd. for C\(_{26}\)H\(_{23}\)NO\(_2\): 381.1729, found 381.1737. Elem. Anal. calcd. for C\(_{26}\)H\(_{23}\)NO\(_2\): C 81.86%, H 6.08%, N 3.67%, found C 81.43%, H 6.04%, N 3.64%.
**Addition of Organozinc Reagents to N-Acyloxyiminium Ions**

1-Ethyl-3,4-dihydroisoquinolin-2(1H)-yl 2,4,6-trimethylbenzoate (33).

Purification by column chromatography (SiO₂; EtOAc/pentane 5:95) afforded compound 33 as a colorless oil which slowly solidified (Rₜ = 0.6). Mp = 81.5-81.8 °C. HPLC on Chiralpak AD column, 4.6 × 250 mm, 10 µm, (n-heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): Rt = 9.1 min (major), Rt = 15.1 min (minor); 60% ee. [α]₀ = + 4.6 (c 0.87, CHCl₃). ¹H-NMR (400 MHz, CDCl₃) δ = 7.09-7.08 (m, 4H), 6.82 (s, 2H), 4.24 (t, J = 5.8 Hz, 1H), 3.74-3.68 (m, 1H), 3.54-3.48 (m, 1H), 3.02-2.99 (m, 2H), 2.28 (s, 6H), 1.97-1.90 (m, 2H), 1.11 (t, J = 7.4 Hz, 3H) ppm. ¹³C-NMR (100 MHz, CDCl₃) δ = 168.5, 139.4, 136.1, 135.0, 133.2, 129.8, 128.5, 128.2, 126.8, 126.3, 126.0, 66.4, 49.4, 27.6, 25.5, 21.1, 19.5, 10.3 ppm. HRMS calcd. for C₂₁H₂₅NO₂: 323.1885, found 323.1890. Elem. Anal. calcd for C₂₁H₂₅NO₂: C 77.98%, H 7.79%, N 4.33%, found C 77.91%, H 7.80%, N 4.33%.

1-Ethyl-3,4-dihydroisoquinolin-2(1H)-yl 2,4,6-triisopropylbenzoate (34).

Purification by column chromatography (SiO₂; EtOAc/pentane 2:98) afforded compound 34 as a colorless oil (Rₜ = 0.4). HPLC on a Chiralpak AD column, 4.6 × 250 mm, 10 µm, (n-heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): Rt = 6.9 min (major), Rt = 7.7 min (minor). 27% ee. [α]₀ = - 3.2 (c 0.37, CHCl₃). ¹H-NMR (400 MHz, CDCl₃) δ = 7.18-7.06 (m, 4H), 6.98 (s, 2H), 4.26 (t, J = 6.0 Hz, 1H), 3.76-3.69 (m, 1H), 3.58-3.52 (m, 1H), 3.08-3.00 (m, 1H), 2.96-2.84 (m, 4H), 1.98-1.86 (m, 2H), 1.24 (t, J = 6.6 Hz, 12H), 1.17-1.12 (m, 9H) ppm. ¹³C-NMR (50 MHz, CDCl₃) δ = 168.9, 150.4, 145.2, 136.2, 133.0, 128.8, 128.4, 127.0, 126.4, 125.9, 120.8, 66.4, 48.7, 34.4, 31.4, 28.1, 25.1, 24.2, 24.1, 23.9, 10.6 ppm. MS-Cl calcd. for C₂₇H₃₇NO₂: 408 [M+H]⁺.

1-Ethyl-3,4-dihydroisoquinolin-2(1H)-yl 2,4,6-dimethoxybenzoate (35).

Purification by column chromatography (SiO₂; EtOAc/pentane 25:75) afforded compound 35 as a colorless oil (Rₜ = 0.4). HPLC on a Chiralpak AD column, 4.6 × 250 mm, 10 µm, (n-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 19.6 min (major), Rt = 32.0 min (minor). 46% ee. [α]₀ = + 7.0 (c 193
0.87, CHCl₃). ¹H-NMR (400 MHz, CDCl₃) δ = 7.70 (d, J = 8.6 Hz, 1H), 7.18-7.10 (m, 4H), 6.46-6.41 (m, 2H), 4.24 (t, J = 6.0 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.69-3.71 (m, 1H), 3.51-3.45 (m, 1H), 3.08-2.92 (m, 2H), 1.99-1.83 (m, 2H), 1.09 (t, J = 7.4 Hz, 3H) ppm. ¹³C-NMR (50 MHz, CDCl₃) δ = 164.7, 164.1, 161.0, 136.7, 137.4, 128.4, 126.9, 126.1, 125.9, 112.0, 104.5, 99.0, 66.2, 55.7, 55.4, 49.1, 27.7, 25.4, 10.5 ppm. MS-CI calcd. for C₂₀H₂₃NO₄: 341 [M+H]⁺. HRMS calcd. for C₁₈H₁₈NO₄ [M-Et]: 312.1236, found 312.1249.

1-Ethyl-3,4-dihydroisoquinolin-2(1H)-yl 2,6-dimethoxybenzoate (36).

Purification by column chromatography (SiO₂; EtOAc/pentane 2:8) afforded compound 36 as a yellow solid (Rₜ = 0.4). Mp = 96.1-97.9 ºC. HPLC on a Chiralpak AD column, 4.6 x 250 mm, 10 µm, (n-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 12.6 min (major), Rt = 19.1 min (minor). 32% ee. [α]D = + 12.9 (c 0.52, CHCl₃). ¹H-NMR (400 MHz, CDCl₃) δ = 7.18-7.07 (m, 4H), 6.83 (s, 2H), 4.42 (br s, 1H), 3.78-3.72 (m, 1H), 3.12-2.98 (m, 2H), 2.31 (s, 6H), 2.27 (s, 3H), 1.60 (t, J = 7.3 Hz, 3H) ppm. ¹³C-NMR (50 MHz, CDCl₃) δ = 168.7, 139.5, 137.4, 135.0, 132.5, 129.6, 128.4, 128.2, 126.5, 126.2, 60.9, 49.8, 26.1, 21.1, 19.6 ppm. HRMS calcd. for C₂₀H₂₅NO₄: 341 [M+H]⁺. HRMS calcd. for C₁₈H₁₈NO₄ [M-Et]: 312.1236, found 312.1237. Elem. Anal. for C₂₀H₂₅NO₄: C 70.36%, H 6.79%, N 4.10%, found C 70.45%, H 6.82%, N 4.06%.

1-Methyl-3,4-dihydroisoquinolin-2(1H)-yl 2,4,6-trimethylbenzoate (39).

Purification by column chromatography (SiO₂; EtOAc/pentane 1:9) afforded compound 39 as a colorless oil (Rₜ = 0.6). HPLC on a Chiralpak AD column, 4.6 x 250 mm, 10 µm, (n-heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): Rt = 13.7 min (major), Rt = 20.6 min (minor); 8% ee. ¹H-NMR (400 MHz, CDCl₃) δ = 7.18-7.07 (m, 4H), 6.83 (s, 2H), 4.42 (br s, 1H), 3.78-3.72 (m, 1H), 3.50-3.44 (m, 1H), 3.12-2.98 (m, 2H), 2.31 (s, 6H), 2.27 (s, 3H), 1.60 (t, J = 6.8 Hz, 3H) ppm. ¹³C-NMR (50 MHz, CDCl₃) δ = 168.7, 139.5, 137.4, 135.0, 132.5, 129.6, 128.4, 128.2, 126.5, 126.2, 60.9, 49.8, 26.1, 21.1, 19.6 ppm. HRMS calcd. for C₂₀H₂₅NO₄: 309.1729, found 309.1736.
Addition of Organozinc Reagents to N-Acyloxyiminium Ions

1-n-Butyl-3,4-dihydroisoquinolin-2(1H)-yl 2,4,6-trimethylbenzoate (41).

Purification by column chromatography (SiO$_2$; EtOAc/pentane 5:95) afforded compound 41 as a colorless oil which slowly solidified ($R_f = 0.5$). HPLC on a Chiralpak AD column, 4.6 × 250 mm, 10 µm, (n-heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): Rt = 8.4 min (major), Rt = 12.3 min (minor); 55% ee. [α]$_D$ = -11.6 (c 0.51, CHCl$_3$). $^1$H-NMR (400 MHz, CDCl$_3$) δ = 7.17-7.07 (m, 4H), 6.81 (s, 2H), 4.29 (t, $J = 6.0$ Hz, 1H), 3.73-3.66 (m, 1H), 3.58-3.52 (m, 1H), 3.07-2.99 (m, 1H), 2.96-2.89 (m, 1H), 2.27 (s, 6H), 2.25 (s, 3H), 1.92-1.79 (m, 2H), 1.69-1.52 (m, 2H), 1.44-1.32 (m, 2H), 0.93 ppm. $^13$C-NMR (50 MHz, CDCl$_3$) δ = 168.5, 139.4, 136.6, 135.1, 133.0, 129.8, 128.5, 128.2, 126.9, 126.3, 126.0, 65.2, 48.8, 35.1, 28.1, 25.0, 22.8, 21.1, 19.5, 14.0 ppm. HRMS calcd. for C$_{23}$H$_{29}$NO$_2$: 351.2198, found 351.2181.

Anthracene-9-carbonyl chloride.$^{22}$

Quantitative yield; yellow solid. $^1$H-NMR (400 MHz, CDCl$_3$) δ = 8.59 (s, 1H), 8.12 (d, $J = 8.8$ Hz, 2H), 8.06 (d, $J = 8.8$ Hz, 2H), 7.66-7.61 ppm. 2,6-Dimethoxybenzoyl chloride.$^{22}$

Quantitative yield; light yellow solid. $^1$H-NMR (400 MHz, CDCl$_3$) δ = 7.35 (t, $J = 8.5$ Hz, 1H), 6.57 (d, $J = 8.5$ Hz, 2H), 3.87 (s, 6H) ppm.
2,4-Dimethoxybenzoyl chloride.\textsuperscript{22}
Quantitative yield; light yellow solid. \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \( \delta = 8.16 \) (d, \( J = 9.0 \) Hz, 1H), 6.55 (dd, \( J_1 = 9.0 \) Hz, \( J_2 = 2.3 \) Hz, 1H), 6.46 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H) ppm.

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\text{Cl} \\
\text{O} \\
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\]

3,5-Dinitrobenzoyl chloride.\textsuperscript{22}
Quantitative yield; light yellow solid. \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \( \delta = 9.35-9.33 \) (m, 1H), 9.25-9.24 (m, 2H) ppm. \textsuperscript{13}C-NMR (50 MHz, CDCl\textsubscript{3}) \( \delta = 165.1, 146.9, 136.4, 130.3, 124.1 \) ppm.

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\text{O}_2\text{N} \\
\\text{NO}_2 \\
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\]

2,4,6-Triisopropylbenzoyl chloride.\textsuperscript{22}
Quantitative yield; white solid. \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \( \delta = 7.04 \) (s, 2H), 3.11-3.01 (m, 2H), 2.95-2.88 (m, 2H), 1.29 (d, \( J = 6.8 \) Hz, 12H), 1.26 (d, \( J = 6.9 \) Hz, 6H) ppm. \textsuperscript{13}C-NMR (50 MHz, CDCl\textsubscript{3}) \( \delta = 171.1, 151.1, 143.0, 153.2, 121.3, 34.4, 31.4, 23.9, 23.8 \) ppm.

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\text{O} \\
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1-(2,4,6-Triisopropylphenyl)propan-1-one.\textsuperscript{23}
Colorless oil. \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \( \delta = 6.99 \) (s, 2H), 2.92-2.85 (m, 1H), 2.72 (q, \( J = 7.2 \) Hz, 2H), 2.65-2.58 (m, 2H), 1.27-1.18 (m, 21H) ppm. \textsuperscript{13}C-NMR (50 MHz, CDCl\textsubscript{3}) \( \delta = 211.9, 149.3, 143.4, 138.2, 121.0, 39.5, 34.3, 31.1, 24.2, 24.0, 7.7 \) ppm. HRMS calcd. for C\textsubscript{18}H\textsubscript{28}O: 260.2140, found 260.2132.
Addition of Organozinc Reagents to N-Acyloxyiminium Ions

5.5 References


Addition of Organozinc Reagents to N-Acloyximinium Ions


18 Bea Macia Ruiz, Maria de los Angeles Fernandez Ibanez, Natasa Mirsc and Bart Stegink are kindly acknowledged for the synthesis of the phosphoramidite ligands L9-L14.


22 Commercially available from Aldrich.
