Chemo- and Regioselective Magnesium-Catalyzed ortho-Alkenylation of Anilines

Adisak Chatupheeraphat,† Magnus Rueping*,‡,† and Marc Magre*,‡

†Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
‡KAUST Catalysis Center (KCC), King Abdullah University of Science and Technology (KAUST), Thuwal 23955-6900, Saudi Arabia

Supporting Information

ABSTRACT: A simple and efficient catalytic system for a chemo- and regioselective ortho- alkenylation of anilines is presented. The new magnesium-catalyzed reaction allows the use of a wide range of alkynes and anilines with different electronic and steric properties and provides free as well as protected anilines with excellent yields.

The insertion of carbon substitutents on aromatic rings is one of the most powerful synthetic methodologies in organic chemistry.1 In particular, the ortho-functionalization of aniline derivatives is a crucial strategy for the derivatization of anilines.2 Transition-metal catalysts have been extensively used in the selective functionalization of aniline derivatives through C–H activation processes.3 Compared to the well-established ortho-arylation of anilides,4 the direct regioselective ortho-alkenylation has been explored less5 and was accomplished with alkynes5a,b and alkenes5c,d as electrophiles (Scheme 1a,b). However, these reactions often require the presence of a directing group on nitrogen, to achieve the ortho-substitution.

As vinyl-substituted anilines are useful intermediates in the synthesis of alkaloids and heterocycles with pharmacological properties,9 improved synthetic methodologies for the ortho-directed alkenylation of anilines are desired. Herein, we present the first catalytic system based on a readily available Mg catalyst, which allows the selective ortho-alkenylation of free anilines in excellent yields and selectivities (Scheme 1c) under relatively mild reaction conditions.

We started our development by investigating various reaction parameters for the Mg-catalyzed reaction of phenylacetylene 1a and aniline 2a (Table 1).

Initially, magnesium complexes such as Mg(ClO$_4$)$_2$ and Mg(OIT)$_2$ were tested as catalysts, affording the desired product 3a in a moderate yield together with the disubstituted byproduct 4 (Table 1, entries 1 and 2, respectively). Less Lewis acidic MgCl$_2$ provided a lower yield (Table 1, entry 3), and Mg(NIT)$_2$ afforded the desired product in a higher yield (Table 1, entry 4). This result can be explained by the effect of the highly delocalized counterion, enhancing the reactivity of the Mg(II) center.10 Generally, hexafluoroisopropanol (HFIP) was found to be a good solvent.10 To increase the catalytic
These results showed that the acidic, protic solvent HFIP is almost no conversion was achieved (Table 1, entries 8 and 9). Next, di-alkyne/aniline ratios (Table 1, entries 6 and 7), and the best nanosized zeolite failed on the coupling of electron de-
formation of disubstituted byproduct (nBu4NPF6) was added to the reaction mixture. Unfortunately, the yield toward our desired product increasing the reaction temperature led to a higher conversion while maintaining the small activity further, tetrabutylammonium hexafluorophosphate (Bu4NPF6) was added to the reaction mixture. Unfortunately, the yield toward the desired product 3a was not improved (Table 1, entry 5 vs entry 4). To suppress the formation of disubstituted byproduct 4, we tested different alkylene/aniline ratios (Table 1, entries 6 and 7), and the best result was obtained using 3 equivalents of aniline (Table 1, entry 7). Next, different solvents were evaluated. However, almost no conversion was achieved (Table 1, entries 8–11). These results showed that the acidic, protic solvent HFIP is beneficial in terms of reactivity. With 5 mol % Mg(NTf2)2, *Yield of the isolated product. With 5 mol % catalyst.*

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>aniline (equiv)</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>3a (%)</th>
<th>4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mg(ClO4)2</td>
<td>1.5</td>
<td>HFIP</td>
<td>40</td>
<td>54</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>Mg(OTf)2</td>
<td>1.5</td>
<td>HFIP</td>
<td>40</td>
<td>47</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>MgCl2</td>
<td>1.5</td>
<td>HFIP</td>
<td>40</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Mg(NTf2)2</td>
<td>1.5</td>
<td>HFIP</td>
<td>40</td>
<td>64</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>Mg(NTf2)2</td>
<td>2</td>
<td>HFIP</td>
<td>40</td>
<td>62</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>Mg(NTf2)2</td>
<td>3</td>
<td>HFIP</td>
<td>40</td>
<td>61</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>Mg(NTf2)2</td>
<td>3</td>
<td>iPrOH</td>
<td>40</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>8</td>
<td>Mg(NTf2)2</td>
<td>3</td>
<td>tBuOH</td>
<td>40</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>9</td>
<td>Mg(NTf2)2</td>
<td>3</td>
<td>dioxane</td>
<td>40</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>10</td>
<td>Mg(NTf2)2</td>
<td>3</td>
<td>DCM</td>
<td>40</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>11</td>
<td>Mg(NTf2)2</td>
<td>3</td>
<td>toluene</td>
<td>40</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>12</td>
<td>Mg(NTf2)2</td>
<td>3</td>
<td>HFIP</td>
<td>60</td>
<td>64</td>
<td>13</td>
</tr>
<tr>
<td>13</td>
<td>Mg(NTf2)2</td>
<td>3</td>
<td>HFIP</td>
<td>70</td>
<td>76</td>
<td>(74)</td>
</tr>
<tr>
<td>14</td>
<td>Mg(NTf2)2</td>
<td>3</td>
<td>HFIP</td>
<td>80</td>
<td>74</td>
<td>11</td>
</tr>
<tr>
<td>15</td>
<td>Mg(NTf2)2</td>
<td>3</td>
<td>HFIP</td>
<td>90</td>
<td>63</td>
<td>7</td>
</tr>
<tr>
<td>16</td>
<td>Mg(NTf2)2</td>
<td>3</td>
<td>HFIP</td>
<td>70</td>
<td>61</td>
<td>8</td>
</tr>
<tr>
<td>17</td>
<td>Mg(NTf2)2</td>
<td>3</td>
<td>HFIP</td>
<td>70</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1a (0.5 mmol), Mg salt (10 mol %), HFIP (1 mL), 40 °C, 24 h. GC yield, using mesitylene as the internal standard. Addition of *Bu4NF (10 mol %). With 5 mol % Mg(NTf2)2. *Yield of the isolated product. With 5 mol % catalyst.*

Subsequently, the substrate scope and limitations for this transformation were studied. Generally, the reactions were carried out with 5 mol % Mg(NTf2)2 at 70 °C for 24 h (Scheme 2). Alkynes with different electronic properties were tolerated, and alkenylated products 3m–v were isolated in good to excellent yields. The same behavior was observed when different substituents were present in the ortho- or meta-positions, affording the corresponding products 3w–3ab in good yields. We were pleased to see that N-substituted amines also underwent ortho-alkenylation in good yields (3ac and 3ad), showing that this catalytic system can alkenylate both, free and N-alkylated aniline derivatives. Strong conjugated substituted aniline 3f was isolated in 52% yield under our conditions. Phenylacetylene 1g containing a boronic acid pinacol ester group, which allows further derivatization, was also tolerated providing 3g in 64% yield. In addition, the highly $\pi$-extended aromatic 1h provided the expected product 3h in good yield. We were also pleased to see that different patterns of substitution of the methyl group on the aromatic ring afforded the corresponding products 3i and 3j in good yields.

Furthermore, substituents with different electronic effects in the meta-position of the aryl acetylene substrate did not affect the activity, affording the desired products 3j–l in good yields. After evaluating the reactivity of different aryl acetylene precursors, we attempted to extend the scope of the Mg(NTf2)2-catalyzed intermolecular ortho-alkenylation reaction by investigating a wide variety of aniline-derived compounds. As shown in Scheme 3, alkanes with different electronic properties, bearing either electron-donating or electron-withdrawing groups in the para-position, were tolerated, and alkenylated products 3m–v were isolated in good to excellent yields. The same behavior was observed when different substituents were present in the ortho- or meta-positions, affording the corresponding products 3w–3ab in good yields. We were pleased to see that N-substituted amines also underwent ortho-alkenylation in good yields (3ac and 3ad), showing that this catalytic system can alkenylate both, free and N-alkylated aniline derivatives. Strong conjugated
aromatic systems such as 1- and 2-naphthyl anilines provided the desired products 3ae and 3af in good yields and selectivities. Finally, when we tested an aniline with both ortho-positions blocked, the reaction provided the corresponding para-substituted product 3ah in good yield.

The practical applicability of the Mg(NTf₂)₂ catalytic system is shown by performing the chemo- and regioselective ortho-alkenylation of aniline 2a at 10 mmol scale (Scheme 4). In this case, ortho-alkenylation aniline 3a could be isolated in 71% yield.

Scheme 4. Large Scale Reaction

![Scheme 4. Large Scale Reaction](image)

From a mechanistic point of view, in principle Lewis acid or Bronsted acid catalysis may occur. Despite the fact that Mg(NTf₂)₂ salt is stable in aqueous or protic media, there is a low likelihood that the catalyst undergoes hydrolysis to generate the corresponding NHTf₂ that acts as a Bronsted acid catalyst. To investigate if our transformation is catalyzed by the Lewis or Bronsted acid, we used 2,6-tert-butylpyridine (ditBuPy) as a noncoordinative base. This base acts as a proton scavenger, suppressing the activity of the Bronsted acid. As depicted in Figure 1, we performed several kinetic experiments using Mg(NTf₂)₂, the corresponding Bronsted acid NHTf₂, and both catalysts in the presence of the proton scavenger, 2,6-tert-butylpyridine. The results show that both Mg(NTf₂)₂ (red line) and the corresponding Bronsted acid

![Figure 1. Reaction profile of Mg(NTf₂)₂ and Bronsted acid-catalyzed ortho-alkenylation of aniline with and without a proton scavenger.](image)

**Scheme 3. Aniline Scope of Mg(II)-Catalyzed ortho-Alkenylation of Aniline**

\[
\text{Ar} = \begin{array}{c}
\text{NO}_2 \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Cl} \\
\text{Me} \\
\text{Me} \\
\text{Ph} \\
\text{CO}_2\text{Me} \\
\text{NH}_2 \\
\end{array}
\]

**Reactions Conditions:**
- \(1\) (0.5 mmol), 2 (1.5 mmol), \(\text{Mg(NTf}_2\text{)}\) (5 mol %) in HFIP (0.5 M) at 70 °C for 24 h. Yield for isolated products.
- Reaction at 60 °C.
- Reaction at 80 °C.

![Scheme 3. Aniline Scope of Mg(II)-Catalyzed ortho-Alkenylation of Aniline](image)
(green line) are active catalysts for the ortho-alkenylation of free aniline. In the presence of the proton scavenger (2,6-tert-butylpyridine), whereas the activity of Mg(NTf₂)₂ is maintained (purple line), the activity of the Brønsted acid (blue line) decreased dramatically. With these results, we suggest that Mg(NTf₂)₂ is the active catalyst for the ortho-alkenylation of free anilines.¹⁵

To provide deeper insight into the catalytic system, we performed deuterium labeling experiments (Scheme 5).

Initially, using HFIP-OD, we found that in the absence of a catalyst, the aromatic ring remained unchanged (Scheme 5a1), which suggests that the aniline itself does not show any nucleophilic character in the presence of HFIP. We also found that in the presence of Mg(NTf₂)₂, both ortho- and para-positions of aniline undergo deuteration (Scheme 5a2), meaning that if the catalyst is present in the reaction media, the nucleophilicity of aniline increases. We also tested the same reaction using MgCl₂ as a catalyst (Scheme 5a3). In this case, only 17% H−D exchange was observed. These results suggest that Mg(NTf₂)₂ enhances the nucleophilicity of aniline. Second, we performed the catalytic reaction under the optimal reaction conditions with HFIP-OD instead of HFIP (Scheme 5b) and found that both ortho- and para-positions of the aniline ring underwent H−D exchange, as well as a D-incorporation at the olefinic site leading to a 1:1 ratio of (E)- and (Z)-d-olefin. We also performed the same reaction, using d₅-aniline and HFIP (Scheme 5c). In this case, we observed also partial D-incorporation at the olefinic site, which is not expected due to the use of HFIP. However, due to the 100% H−D exchange from the d₅-aniline and solvent (Scheme 5a4), 3 equivalents of HFIP-OD are produced in the reaction media; therefore, a low percentage of D incorporation is observed.

Gandon and Lebœuf have recently reported a Ca(II)-catalyzed hydroamination of alkenes using HFIP as the solvent.¹¹c,₁₆ The authors stated that the crucial role of the solvent, when coordinated to Ca(NTf₂)₂, is to activate the alkene.

On the basis of this observation and our results, we propose a mechanism for the Mg(NTf₂)₂-catalyzed ortho-alkenylation of anilines (Scheme 6). First, HFIP coordinates to Mg(NTf₂)₂, providing an active species A. Subsequently, coordination and activation of the alkene and aniline take place. Whereas the basic site of the ligand activates the aniline for electrophilic substitution, Mg(II)−HFIP complex A activates the alkyne (TS1), affording the corresponding compound B, which undergoes rearomatization, providing the corresponding ortho-alkenylated aniline product C. At the same time, Mg(II) complex D regenerates, in the presence of HFIP, the active catalytic species A.

To summarize, we have developed an efficient and selective method for the ortho-alkenylation of free as well as N-substituted anilines. For the first time, excellent selectivities and good-to-excellent yields have been achieved under...
homogeneous Lewis acid catalysis. Moreover, under mild reaction conditions, a wide range of alkenes and anilines with different electronic and steric properties are tolerated. Thus, the newly developed procedure competes favorably with different reports in the literature, which mostly require elevated temperatures and display a more narrow substrate scope. By using 2,6-tert-butylpyridine as a proton scavenger, we confirmed that Mg(NTf$_2$)$_2$ acts as a Lewis acid catalyst for our transformation. Furthermore, by means of D-labeling experiments, we obtained a deeper inside into the mechanism of the transformation that helped to explain the new magnesium catalysis.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-XXX-9803526.

Detailed characterization of products and $^1$H and $^{13}$NMR spectra (PDF)

**AUTHOR INFORMATION**

**Corresponding Authors**

*E-mail: magnus.rueping@rwth-aachen.de.

*E-mail: marc.magre@oc.rwth-aachen.de.

**ORCID**

Magnus Rueping: 0000-0003-4580-5227

Marc Magre: 0000-0002-5950-4129

**Notes**

The authors declare no competing financial interest.

**REFERENCES**


(17) During the preparation of the manuscript, Gandon and Leboeuf reported a Ca(NTf$_2$)$_2$:Bu$_4$NPF$_6$-catalyzed hydroarylation of electron deficient styrenes using HFIP as a solvent: Qi, C.; Gandon, V.; Leboeuf, D. Angew. Chem., Int. Ed. 2018, 57, 14245.