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

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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.

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

The insertion of carbon substituents 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 alkynes^{5a,b} and alkenes^{5c,d} as electrophiles (Scheme 1a,b). However, these reactions often require the presence of a directing group on nitrogen, to achieve the *ortho*-substitution.

Scheme 1. Overview of the Homogeneous Catalytic Systems for the *ortho*-Alkenylation of Anilines

Transition Metal Catalyzed Reactions

Selective *ortho*-alkenylation
Efficient for electron rich, neutral and
electron deficient alkynes and anilines

The *ortho*-alkenylation of free anilines is rather challenging⁶ as free amines often inhibit the reactivity resulting in limited protocols. The electrophilic activation of organic molecules by Lewis acid catalysis constitutes an important method for the synthesis of fine chemicals.⁷ The use of metal triflates and triflimidates [MOTf_n or M(NTf₂)_n] has been examined for C–C and C–heteroatom bond formation.⁸ To the best of our knowledge, there is no report in the literature on an alkali earth-metal triflate- or triflimidate-catalyzed regioselective functionalization of free anilines.

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(ClO₄)₂ and Mg(OTf)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 MgCl₂ provided a lower yield (Table 1, entry 3), and Mg(NTf₂)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 counteranion, enhancing the reactivity of the Mg(II) center.^{8b} Generally, hexafluoroisopropanol (HFIP) was found to be a good solvent.¹⁰ To increase the catalytic

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Table 1. Optimization of Mg(II)-Catalyzed *ortho*-Directed Alkenylation of Aniline^a

entry	catalyst	aniline (equiv)	solvent	temp (°C)	yield ^b (%)	
					3a	4
1	Mg(ClO ₄) ₂	1.5	HFIP	40	54	23
2	Mg(OTf) ₂	1.5	HFIP	40	47	21
3	MgCl ₂	1.5	HFIP	40	7	0
4	Mg(NTf ₂) ₂	1.5	HFIP	40	64	35
5 ^c	Mg(NTf ₂) ₂	1.5	HFIP	40	62	36
6	Mg(NTf ₂) ₂	2	HFIP	40	62	20
7	Mg(NTf ₂) ₂	3	HFIP	40	61	10
8	Mg(NTf ₂) ₂	3	ⁱ PrOH	40	<5	<5
9	Mg(NTf ₂) ₂	3	dioxane	40	<5	<5
10	Mg(NTf ₂) ₂	3	DCM	40	<5	<5
11	Mg(NTf ₂) ₂	3	toluene	40	<5	<5
12 ^d	Mg(NTf ₂) ₂	3	HFIP	60	64	13
13 ^d	Mg(NTf ₂) ₂	3	HFIP	70	76 (74) ^e	11
14 ^d	Mg(NTf ₂) ₂	3	HFIP	80	74	11
15 ^f	Ca(NTf ₂) ₂	3	HFIP	70	63	7
16 ^f	HNTf ₂	3	HFIP	70	61	8
17	—	3	HFIP	70	<5	<5

^aReaction conditions: **1a** (0.5 mmol), Mg salt (10 mol %), HFIP (1 mL), 40 °C, 24 h. ^bGC yield, using mesitylene as the internal standard. ^cAddition of ⁿBu₄NPF₆ (10 mol %). ^dWith 5 mol % Mg(NTf₂)₂. ^eYield of the isolated product. ^fWith 5 mol % catalyst.

activity further, tetrabutylammonium hexafluorophosphate (ⁿBu₄NPF₆) was added to the reaction mixture.¹¹ 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 alkyne/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.^{10,12} We also observed that increasing the reaction temperature led to a higher conversion toward our desired product **3a** while maintaining the small amount of disubstituted byproduct **4** (Table 1, entries 12–14), the best result being obtained at 70 °C (74% yield, Table 1, entry 13). When other catalysts were tested (Table 1, entries 15 and 16), we observed a reactivity slightly lower than that of Mg(NTf₂)₂. It is important to highlight that Mg(NTf₂)₂ not only is slightly more active than its corresponding Brønsted acid but also presents the advantage of easy handling. A control experiment showed that Mg(NTf₂)₂ is essential for achieving high levels of conversion (Table 1, entry 17).

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 tested and afforded the corresponding products **3a–f** in good yields.

Because the *ortho*-alkenylation of free anilines using a nanosized zeolite failed on the coupling of electron deficient alkynes,^{6b} it is worth mentioning that electron deficient vinyl-

Scheme 2. Acetylene Scope of Mg(II)-Catalyzed *ortho*-Alkenylation of Aniline^a

^aReaction conditions: **1** (0.5 mmol), **2a** (1.5 mmol), Mg(NTf₂)₂ (5 mol %) in HFIP (0.5 M) at 70 °C for 24 h. Yield for isolated products. ^bReaction at 60 °C. ^cReaction at 100 °C.

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 π -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, anilines 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

Scheme 3. Aniline Scope of Mg(NTf₂)₂-Catalyzed *ortho*-Alkenylation of Aniline^a

^aReaction conditions: **1a** (0.5 mmol), **2** (1.5 mmol), Mg(NTf₂)₂ (5 mol %) in HFIP (0.5 M) at 70 °C for 24 h. Yield for isolated products. ^bReaction at 60 °C. ^cReaction at 80 °C.

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*-alkenylated aniline **3a** could be isolated in 71% yield.

Scheme 4. Large Scale Reaction

From a mechanistic point of view, in principle Lewis acid or Brønsted 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 Brønsted acid catalyst.¹³ To investigate if our transformation is catalyzed by the Lewis or Brønsted acid, we used 2,6-*tert*-butylpyridine (di^tBuPy)¹⁴ as a noncoordinative base. This base acts as a proton scavenger, suppressing the activity of the Brønsted acid. As depicted in Figure 1, we performed several kinetic experiments using Mg(NTf₂)₂, the corresponding Brønsted 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 Brønsted acid

Figure 1. Reaction profile of Mg(NTf₂)₂ and Brønsted acid-catalyzed *ortho*-alkenylation of aniline with and without a proton scavenger. Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), catalyst (5 mol %) in HFIP (0.5 M) at 70 °C, di^tBuPy (20 mol %). Yields determined by GC using mesitylene as the internal standard.

(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 $\text{Mg}(\text{NTf}_2)_2$ is maintained (purple line), the activity of the Brønsted acid (blue line) decreased dramatically. With these results, we suggest that $\text{Mg}(\text{NTf}_2)_2$ 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).

Scheme 5. Deuterium Labeling Experiments

a) Aniline deuteration

b) D-labeling using OD-HFIP

c) D-labeling using d5-aniline

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 $\text{Mg}(\text{NTf}_2)_2$, 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 MgCl_2 as a catalyst (Scheme 5a3). In this case, only 17% H–D exchange was observed. These results suggest that $\text{Mg}(\text{NTf}_2)_2$ 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 on 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 *d*₅-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 *d*₅-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 Leboeuf have recently reported a $\text{Ca}(\text{II})$ -catalyzed hydroamination of alkenes using HFIP as the solvent.^{11c,16} The authors stated that the crucial role of the solvent, when coordinated to $\text{Ca}(\text{NTf}_2)_2$, is to activate the alkene.

On the basis of this observation and our results, we propose a mechanism for the $\text{Mg}(\text{NTf}_2)_2$ -catalyzed *ortho*-alkenylation of anilines (Scheme 6). First, HFIP coordinates to $\text{Mg}(\text{NTf}_2)_2$,

Scheme 6. Proposed Mechanism for $\text{Mg}(\text{NTf}_2)_2$ -Catalyzed *ortho*-Alkenylation of Aniline

providing an active species A. Subsequently, coordination and activation of the alkyne and aniline take place. Whereas the basic site of the ligand activates the aniline for electrophilic substitution, $\text{Mg}(\text{II})$ –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, $\text{Mg}(\text{II})$ 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 alkynes 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 $\text{Mg}(\text{NTf}_2)_2$ acts as a Lewis acid catalyst for our transformation. Furthermore, by means of D-labeling experiments, we obtained a deeper insight into the mechanism of the transformation that helped to explain the new magnesium catalysis.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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