Synthesis of Tertiary Enamides by Ag$_2$CO$_3$-promoted Pd-Catalyzed Alkenylation of Acyclic Secondary Amides.

Arnaud Delforge,† Irene Georgiou,† Adrian Kremer,† Johan Wouters† and Davide Bonifazi*,†

†Namur Research College (NARC) and Department of Chemistry, University of Namur (UNamur), Rue de Bruxelles 61, B-5000, Namur, BE; † School of Chemistry, Cardiff University, Park Place, Main Building, CF10 3AT, Cardiff, UK.

ABSTRACT: A Pd-catalyzed methodology for the preparation of tertiary enamides from acyclic secondary amides and bromo acrylates under mild reaction conditions has been developed using [Pd$_2$(dba)$_3$], XantPhos and Ag$_2$CO$_3$ as a base. The reaction occurs through a stereospecific metal-mediated oxidative-insertion mechanism.

In the last decade, metal-catalyzed C(sp$^2$)-N and C(sp)-N bond-forming reactions with amines and amides have been under great development. In particular, the elaboration of novel alkenylation reactions affording enamides has attracted a lot of attention, as these functional groups are fundamental components of a large variety of natural products and versatile precursors of $\beta$-amino acids, the latter being important building blocks for preparing biologically active peptides, small-molecule pharmaceuticals and chiral synthons. With respect to metal-free protocols (e.g. acid-catalyzed condensation of amides and aldehydes, acylation of imines, Curtius rearrangement of $\alpha,\beta$-unsaturated acyl azides, addition of amides to alkynes, condensation of aldehydes or ketones with nitriles, elimination of $\beta$-hydroxy-$\alpha$-silyl amides, and electroorganic synthesis), metal-catalyzed alkenylation reactions have provided access to substituted enamides in high yields with a full stereocontrol on the double bond (Scheme 1b). Among the recently described methods, Pd- and Cu-catalyzed coupling of alkenyl halides with amides are certainly very efficient. Following the first report by Ogawa and Suzuki describing the stereospecific synthesis of enamides and enimides from vinyl bromides and potassium amides in the presence of a stoichiometric amount of Cul, the groups of Buckwald, Porco, and Mar$^5$ have developed efficient Cu(I)-catalyzed variants that dramatically increase the scope and the chemical compatibility of these coupling reactions (Scheme 1b, eq 1) also starting from lactames (Scheme 1b, eq 2). Following the first protocols by Mori and Kozawa describing intramolecular Pd-catalyzed vinylation of $\beta$-lactams, versatile Pd-catalyzed variants have been also developed by Wallace and co-workers, and later by Willis, who reported the synthesis of tertiary enamides (Scheme 1b, eq 2) through a coupling reaction between an enol triflate and amides, carbamates or sulfonamides.

Scheme 1. Metal-free (a) and metal-catalyzed (b) synthetic approaches for preparing enamides.

**Scheme 1a.**

**Scheme 1b.**

---

$[^1]$ Namur Research College (NARC) and Department of Chemistry, University of Namur (UNamur), Rue de Bruxelles 61, B-5000, Namur, BE; † School of Chemistry, Cardiff University, Park Place, Main Building, CF10 3AT, Cardiff, UK.

**ABSTRACT:** A Pd-catalyzed methodology for the preparation of tertiary enamides from acyclic secondary amides and bromo acrylates under mild reaction conditions has been developed using [Pd$_2$(dba)$_3$], XantPhos and Ag$_2$CO$_3$ as a base. The reaction occurs through a stereospecific metal-mediated oxidative-insertion mechanism.

In the last decade, metal-catalyzed C(sp$^2$)-N and C(sp)-N bond-forming reactions with amines and amides have been under great development. In particular, the elaboration of novel alkenylation reactions affording enamides has attracted a lot of attention, as these functional groups are fundamental components of a large variety of natural products and versatile precursors of $\beta$-amino acids, the latter being important building blocks for preparing biologically active peptides, small-molecule pharmaceuticals and chiral synthons. With respect to metal-free protocols (e.g. acid-catalyzed condensation of amides and aldehydes, acylation of imines, Curtius rearrangement of $\alpha,\beta$-unsaturated acyl azides, addition of amides to alkynes, condensation of aldehydes or ketones with nitriles, elimination of $\beta$-hydroxy-$\alpha$-silyl amides, and electroorganic synthesis), metal-catalyzed alkenylation reactions have provided access to substituted enamides in high yields with a full stereocontrol on the double bond (Scheme 1b). Among the recently described methods, Pd- and Cu-catalyzed coupling of alkenyl halides with amides are certainly very efficient. Following the first report by Ogawa and Suzuki describing the stereospecific synthesis of enamides and enimides from vinyl bromides and potassium amides in the presence of a stoichiometric amount of Cul, the groups of Buckwald, Porco, and Mar$^5$ have developed efficient Cu(I)-catalyzed variants that dramatically increase the scope and the chemical compatibility of these coupling reactions (Scheme 1b, eq 1) also starting from lactames (Scheme 1b, eq 2). Following the first protocols by Mori and Kozawa describing intramolecular Pd-catalyzed vinylation of $\beta$-lactams, versatile Pd-catalyzed variants have been also developed by Wallace and co-workers, and later by Willis, who reported the synthesis of tertiary enamides (Scheme 1b, eq 2) through a coupling reaction between an enol triflate and amides, carbamates or sulfonamides.

---

$[^1]$ Namur Research College (NARC) and Department of Chemistry, University of Namur (UNamur), Rue de Bruxelles 61, B-5000, Namur, BE; † School of Chemistry, Cardiff University, Park Place, Main Building, CF10 3AT, Cardiff, UK.

**ABSTRACT:** A Pd-catalyzed methodology for the preparation of tertiary enamides from acyclic secondary amides and bromo acrylates under mild reaction conditions has been developed using [Pd$_2$(dba)$_3$], XantPhos and Ag$_2$CO$_3$ as a base. The reaction occurs through a stereospecific metal-mediated oxidative-insertion mechanism.

In the last decade, metal-catalyzed C(sp$^2$)-N and C(sp)-N bond-forming reactions with amines and amides have been under great development. In particular, the elaboration of novel alkenylation reactions affording enamides has attracted a lot of attention, as these functional groups are fundamental components of a large variety of natural products and versatile precursors of $\beta$-amino acids, the latter being important building blocks for preparing biologically active peptides, small-molecule pharmaceuticals and chiral synthons. With respect to metal-free protocols (e.g. acid-catalyzed condensation of amides and aldehydes, acylation of imines, Curtius rearrangement of $\alpha,\beta$-unsaturated acyl azides, addition of amides to alkynes, condensation of aldehydes or ketones with nitriles, elimination of $\beta$-hydroxy-$\alpha$-silyl amides, and electroorganic synthesis), metal-catalyzed alkenylation reactions have provided access to substituted enamides in high yields with a full stereocontrol on the double bond (Scheme 1b). Among the recently described methods, Pd- and Cu-catalyzed coupling of alkenyl halides with amides are certainly very efficient. Following the first report by Ogawa and Suzuki describing the stereospecific synthesis of enamides and enimides from vinyl bromides and potassium amides in the presence of a stoichiometric amount of Cul, the groups of Buckwald, Porco, and Mar$^5$ have developed efficient Cu(I)-catalyzed variants that dramatically increase the scope and the chemical compatibility of these coupling reactions (Scheme 1b, eq 1) also starting from lactames (Scheme 1b, eq 2). Following the first protocols by Mori and Kozawa describing intramolecular Pd-catalyzed vinylation of $\beta$-lactams, versatile Pd-catalyzed variants have been also developed by Wallace and co-workers, and later by Willis, who reported the synthesis of tertiary enamides (Scheme 1b, eq 2) through a coupling reaction between an enol triflate and amides, carbamates or sulfonamides.

---

$[^1]$ Namur Research College (NARC) and Department of Chemistry, University of Namur (UNamur), Rue de Bruxelles 61, B-5000, Namur, BE; † School of Chemistry, Cardiff University, Park Place, Main Building, CF10 3AT, Cardiff, UK.

**ABSTRACT:** A Pd-catalyzed methodology for the preparation of tertiary enamides from acyclic secondary amides and bromo acrylates under mild reaction conditions has been developed using [Pd$_2$(dba)$_3$], XantPhos and Ag$_2$CO$_3$ as a base. The reaction occurs through a stereospecific metal-mediated oxidative-insertion mechanism.

In the last decade, metal-catalyzed C(sp$^2$)-N and C(sp)-N bond-forming reactions with amines and amides have been under great development. In particular, the elaboration of novel alkenylation reactions affording enamides has attracted a lot of attention, as these functional groups are fundamental components of a large variety of natural products and versatile precursors of $\beta$-amino acids, the latter being important building blocks for preparing biologically active peptides, small-molecule pharmaceuticals and chiral synthons. With respect to metal-free protocols (e.g. acid-catalyzed condensation of amides and aldehydes, acylation of imines, Curtius rearrangement of $\alpha,\beta$-unsaturated acyl azides, addition of amides to alkynes, condensation of aldehydes or ketones with nitriles, elimination of $\beta$-hydroxy-$\alpha$-silyl amides, and electroorganic synthesis), metal-catalyzed alkenylation reactions have provided access to substituted enamides in high yields with a full stereocontrol on the double bond (Scheme 1b). Among the recently described methods, Pd- and Cu-catalyzed coupling of alkenyl halides with amides are certainly very efficient. Following the first report by Ogawa and Suzuki describing the stereospecific synthesis of enamides and enimides from vinyl bromides and potassium amides in the presence of a stoichiometric amount of Cul, the groups of Buckwald, Porco, and Mar$^5$ have developed efficient Cu(I)-catalyzed variants that dramatically increase the scope and the chemical compatibility of these coupling reactions (Scheme 1b, eq 1) also starting from lactames (Scheme 1b, eq 2). Following the first protocols by Mori and Kozawa describing intramolecular Pd-catalyzed vinylation of $\beta$-lactams, versatile Pd-catalyzed variants have been also developed by Wallace and co-workers, and later by Willis, who reported the synthesis of tertiary enamides (Scheme 1b, eq 2) through a coupling reaction between an enol triflate and amides, carbamates or sulfonamides.
Apart from the alkylation of secondary enamides, methods for directly accessing to tertiary enamides through direct alkylation of acyclic amides under mild conditions are deficient (Scheme 1b, eq 3). This limits the versatility of tertiary enamides as valuable stable variants of enamines to be employed in the synthesis of natural products and heterocyclic compounds of biological relevance. Here, we thus describe the synthesis of tertiary N-alkyl and N-aryl enamides through metal-catalyzed alkenylation reaction between acyclic secondary amides and β-halo acrylates and β-halo acrylonitriles (Scheme 1b-ii). As a matter of fact, this method is an effective strategy for synthesizing tri-substituted vinylogous imides and vinylogous N-acyl amino-nitriles.

Table 1. Optimization of the Pd-catalyzed cross-coupling reaction between N-Methyl propionamide and (E)-3-Bromo-methylacrylate.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>base</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Pd(dba)2]</td>
<td>Cs2CO3</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>[Pd(dba)2]</td>
<td>K2CO3</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>[Pd(dba)2]</td>
<td>Na2CO3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>[Pd(dba)2]</td>
<td>Ag2CO3</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>[Pd(dba)2]</td>
<td>Ag2CO3</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>[Pd(dba)2]</td>
<td>Ag2CO3</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>Ag2CO3</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

*Reaction conditions: N-methyl propionamide (0.3 mmol), (E)-3-bromo-methylacrylate (0.25 mmol), catalyst (5 mol %), ligand (15 mol %), base (0.35 mmol), MS 3 Å, THF. All yields refer to the isolated compound (SI). All gave full conversion.*

When the acryl bromide was switched to the chloro and iodo analogues (Table 2), enamide (Z)-2 was formed in 62% and 79% yield respectively. In contrast, the fluoro precursor gave no sign of desired enamide (Z)-2. Take together, these results promoted us to exclude an addition-elimination mechanism and are fully consistent with a metal-mediated oxidative-insertion mechanism. Having in hand the optimized reaction conditions and the fundamental mechanistic insights, the attention was then focused in examining the generality of this method, by varying both the vinyl and the amide substrates.

Table 2. Effect of the halide on the cross-coupling reaction using and (Z)-3-halo-ethylacrylate.

<table>
<thead>
<tr>
<th>X</th>
<th>conversion (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cl</td>
<td>100</td>
<td>62</td>
</tr>
<tr>
<td>Br</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>I</td>
<td>100</td>
<td>79</td>
</tr>
</tbody>
</table>

When the acryl bromide was switched to the chloro and iodo analogues (Table 2), enamide (Z)-2 was formed in 62% and 79% yield respectively. In contrast, the fluoro precursor gave no sign of desired enamide (Z)-2. Take together, these results promoted us to exclude an addition-elimination mechanism and are fully consistent with a metal-mediated oxidative-insertion mechanism. Having in hand the optimized reaction conditions and the fundamental mechanistic insights, the attention was then focused in examining the generality of this method, by varying both the vinyl and the amide substrates. As outlined in Scheme 2 (the E and Z notations are omitted for clarity reasons), a variety of tertiary N-alkyl and N-aryl enamides have been prepared employing the Ag2CO3-promoted Pd-catalyzed conditions from moderate to good yields. N-Methyl, -phenyl and -penty1 substituted amides were all successfully coupled to acrylic bromides, and the obtained yield confirmed the steric trend, with the N-pentyl substrate being the less reactive. For example, when (E)-3-bromo-methylacrylate was reacted with the relevant amide,
enamides 5 and 6 were obtained in 83%, 63% and 33% yield, respectively. In general, when the N-pentyl-based amide is coupled with any acyclic acrylic substrate, tertiary enamides with modest yields at around 30% were obtained (enamides 6, 11, 16 and 17). As observed for (E)-1 and (Z)-2, the geometry of the double bond in the acryl halides has a modest effect on the yield. In particular when (Z)-3-bromo-ethylacrylate was used instead of (E)-3-bromo-ethylacrylate, the E isomer of the relevant enamide was obtained vs the Z isomer in the second case, with only slightly higher yield ((E)-1 83% vs (Z)-2 70%). This is further confirmed when comparing the outcome of the reaction leading to the formation of enamides 3 vs 4 and 6 vs 19. Notably, the protocol is also effective for the electronically-rich acrylic derivatives, such as 3-methyl and 3-methoxy substrates, which gave rise to enamides 8-11 and 12-16, respectively. It is worth pointing out that, these reaction conditions are certainly compatible with the majority of thermally unstable and volatile vinyl bromides. The method could be extended to functional substrates as 5-(bromo-methylene)-1,3-dioxolan-4-one (molecule 22, see SI for its synthesis), a potential precursor for preparing 3-amino α-ketoacids. When the 1,3-dioxolan-4-one was reacted with N-pentyl amide, enamide 20 was isolated in 66% yield.

**Scheme 2.** Pd-catalyzed Ag$_2$CO$_3$-promoted formation of acyclic tertiary enamides.


Attempting to elucidate the double bond configuration of one of the tertiary enamides bearing a trisubstituted vinyl group, two types of crystals (rod- and rhombic-like) deriving from the crystallization of product 20 (being the only solid derivative) were obtained and analyzed by single X-ray diffraction (Figure 1). The first proved to be the Z isomer of enamide 20 ((Z)-20, Scheme 3) and, to our surprise, the second crystals resulted from dispiro derivative 21 featuring a central cyclobutane ring (Figure 1). Notably, no crystals of isomer (E)-20 were found. Re-dissolution of the crystals in non-acidic CDCl$_3$ gave the same $^1$H-NMR spectrum as that obtained before crystallization, namely that of 20 with no sign of the typical proton resonances of the cyclobutyl ring, suggesting that the dispiro derivative persists in solution and can be isolated only at the solid state. Complementary variable temperature (VT) $^1$H-NMR investigations of a CDCl$_3$ solution containing 20 show coalescence between 5 and -10 °C of the proton resonances in the diagnostic enamidic chemical shift region, suggesting the presence of a dynamic equilibrium (see SI, Figure 5). Unfortunately, the overlap with the aromatic proton resonances hampers the univocal assignment of the coalescing peaks (see SI, Figure 5). However, when similar VT investigations were performed with enamide 9 (see also 13, SI Figures 1 and 6), the $^1$H-NMR spectrum at rt displayed a vinylic proton resonance at 7.27 ppm that, upon cooling to -40 °C, shifts and clearly splits into two peaks centered at 7.19 and 6.72 ppm, respectively. Likely, these peaks correspond to the vinylic proton resonances of isomers (E)-20 and (Z)-20. In contrast, the VT $^1$H-NMR spectra of all enamides bearing doubly-substituted acryl (e.g., 4, (E)-1 or (Z)-2, Figure SI.7) and of the Br-derived acrylate precursors (see SI, Figures 3-4) displayed no coalescence of the vinylic proton resonances. These observations prompted us to hypothesize that the enamides bearing acryl moieties decorated with EDGs (Me or OMe) undergo E/Z isomerization in solution, and therefore the products are obtained as isomeric mixtures at rt. Likely, this could hypothetically occur through the formation of a dispiro cyclobutane species that serve as intermediate of a fast dynamic equilibrium possibly involving sequential ring-opening and ring-closure
appealing to organic chemists. amino-nitriles, mediated by a dispiro cyclobutane intermediate.

2 derivative 21 as determined by X-ray analysis (space bromides and sterically-encumbered promoted Pd-catalyzed alkenylation procedure providing favored by the presence of Ag-versatility of the method. The reaction likely undergoes showed that the enamides bearing acryl moieties decorated Figure 1. ORTEP representation of (E)-20 and cyclobutyl derivative 21 as determined by X-ray analysis (space group: P21/c). Atomic displacement parameters, obtained at 223K, are drawn at the 30% probability level.


In conclusion, we have demonstrated an Ag$_2$CO$_3$-promoted Pd-catalyzed alkenylation procedure providing access to acyclic tertiary enamides starting from acryl bromides and sterically-encumbered N-substituted amides. A wide range of enamides was synthesized, proving the versatility of the method. The reaction likely undergoes through a stereospecific oxidative-insertion mechanism favored by the presence of Ag$_2$CO$_3$. VT H-NMR experiments showed that the enamides bearing acryl moieties decorated with EDGs undergo E/Z isomerization in solution. The ease of access towards tri-substituted vinylogous imides and N-acyl amino-nitriles makes this Pd-catalyzed alkenylation method appealing to organic chemists.

ASSOCIATED CONTENT

Supporting Information

Synthetic protocols and spectroscopic data, relevant X-ray data for molecules (E)-20 and 21. VT H-NMR spectra of all enamides. The Supporting Information is available free of charge at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author* E-mail: bonifazid@cardiff.ac.uk

ACKNOWLEDGMENT

The authors gratefully acknowledge the EU through the ERC Starting Grant “COLORLANDS” and the FRS-FNRS. We thank Prof. A. Krief (University of Namur) for the useful discussion.

REFERENCES


