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Palladium-Catalyzed Aerobic Oxidative Carbonylation of Alkynes with Amines: A General Access to Substituted Maleimides

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A catalytic oxidative carbonylation reaction was developed for the synthesis of polysubstituted maleimides from alkynes and amines with air as green oxidant. This novel transformation proceeds in the presence of palladium chloride without need for expensive ligands or additives and has a broad substrate scope affording a variety of maleimides in good to high yields.

Substituted maleimides represent interesting building blocks which are widely found in bioactive natural products and drug molecules (Figure 1).[1] In addition, this class of compounds are also applied in engineering,[2, 3] natural rubbers,[4] resins,[5] and the aerospace industry.[6] In general, the traditional industrial process for manufacturing maleimides is the reaction of amines with maleic and related anhydrides. However, this methodology is mainly used for the preparation of non- or symmetrically substituted maleimides.[7] Consequently, there is still a need for new procedures to access polysubstituted maleimides.

As one of the most important homogenous catalytic processes, transition-metal-catalyzed carbonylation reactions allow for direct conversion of easily available feedstocks, like olefins or alkynes and carbon monoxide, into a variety of carbonylated compounds with higher value, which are useful in organic synthesis, pharmaceutical as well as medicinal chemistry.[8] In 2006, Kondo and co-workers reported an interesting ruthenium-catalyzed co-cyclization of internal alkynes, isocyanates, and CO for the synthesis of multiple substituted maleimides in excellent yields (Scheme 1, a).[9a] Later on, $Fe(CO)_5$ was also found to be a good catalyst for this transformation albeit with lower yield (Scheme 1, a).[9b] In the past decade, our group also developed iron and rhodium catalysts which allow for carbonylation of internal alkynes with amines, affording a variety of maleimides (Scheme 1, b).[10] However, as a general drawback only internal alkynes could be applied in these methodologies.

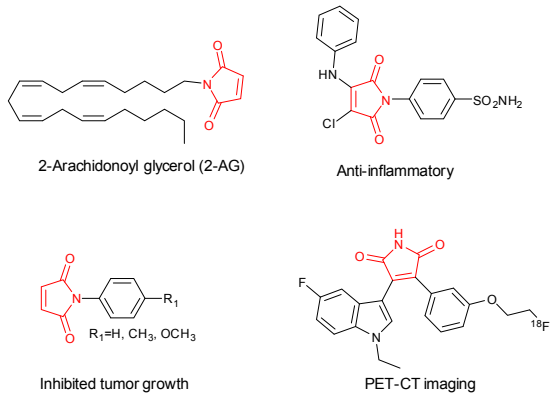

Figure 1. Selective examples of bioactive maleimides.

Recently, we and other groups became interested in the oxidative carbonylation of olefins and alkynes.[11] We thought the later reaction offers a more practical approach to this interesting class of products (Scheme 1, c). Notably, oxidative carbonylations are among the most important reactions in the field of palladium catalysis, since their discovery by Tsuji and co-workers in 1964.[12] Although these transformations have found varied use,[13] the main drawback is the use of (over)stoichiometric amounts of oxidants and/or additional copper salts. Clearly, among all the known oxidants air is the ideal, green reagent. Herein, we report the first general Pd-catalyzed oxidative carbonylation of alkynes with amines in the presence of air for the synthesis of various maleimides in high yields.

In our initial studies we investigated the oxidative carbonylation of phenylacetylene **1a** and aniline **2a** as a benchmark system. Although carbon monoxide is an abundant and inexpensive C1 source, its use under oxidative conditions requires certain safety measures. Hence, all catalytic reactions

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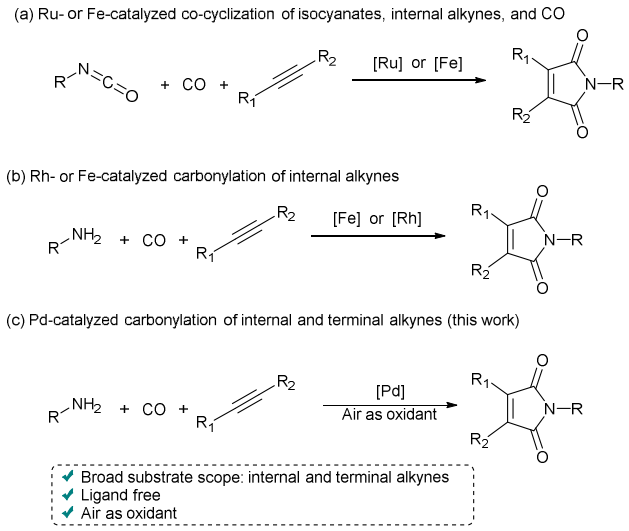
should be performed either with a diluted amount of CO or in the presence of a significant excess carbon monoxide. After variation of solvents, palladium precursors, temperature, and pressure, we found that simple $PdCl_2$ (2.0 mol%) in the presence of air (5 bar) gave the desired product 1,3-diphenyl-1H-pyrrole-2,5-dione **3aa** in 92% GC yield at 120 °C in toluene. Surprisingly, there is almost no by-product observed in this reaction. Obviously, a control experiment without palladium salt revealed no desired product. At the same time, we found that this transformation does not require any ligands, which makes the reaction system very convenient.

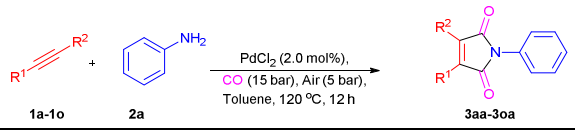


Scheme 1 Synthesis of substituted maleimides via carbonylation reactions

With these optimized conditions in hands, we proceeded to explore the substrate scope for this novel methodology. First, different alkynes including terminal and internal alkynes were studied with aniline as the reaction partner, affording a variety of poly-substituted maleimides in good to high yields (63-92%). As shown in Table 1, the reactions of aromatic terminal alkynes with electron-donating (**1b**) or electron-withdrawing (**1c**-**1f**) functional groups afforded the corresponding products in a straightforward manner. Notably, this reaction tolerates halide substituents (chloride, bromide). In general, substrates bearing electron-withdrawing functional groups gave higher yields compared to electron-rich aryl acetylenes. For aromatic internal alkynes **(1g)**, the yield decreased, and about 35% of the original alkyne remained. On the other hand, aliphatic terminal alkynes with different carbon chains (**1h**-**1l**) afforded the desired products in good yields (81-92%). It is worth noting that internal alkynes (**1m, 1n)** were also transformed affording the multiple-substituted maleimides in good yields.

Next, the scope with respect to amines was investigated and the results are summarized in Table 2. Aromatic amines **(2b-2h)** with either electron-donating **(OMe, Me)** or electron-withdrawing **(F, Cl, Br, CF_3)** functional groups on the phenyl ring provided the corresponding products **(3ab-3ah)** in high yields (71-95%).

Table 1 Pd-catalyzed oxidative aminocarbonylation of alkynes: Variation of alkynes.[a]



1a-1o 2a 3aa-3oa

Entry	Alkynes	Product	Yield/%
1	1a	3aa	92
2	1b	3ba	74
3	1c	3ca	85
4	1d	3da	83
5	1e	3ea	84
6	1f	3fa	87
7	1g	3ga	63
8	1h	3ha	87
9	1i	3ia	91
10	1j	3ja	92
11	1k	3ka	91
12	1l	3la	81

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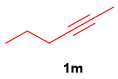
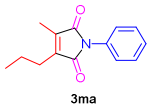
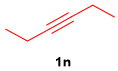
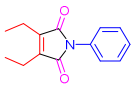
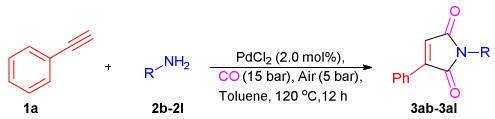
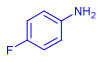
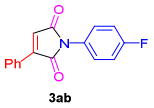
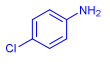
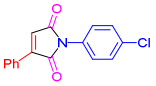
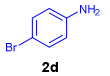
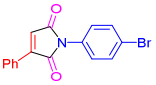
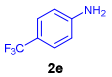
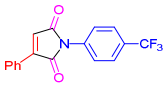
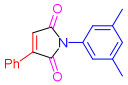
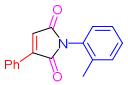
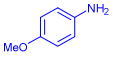
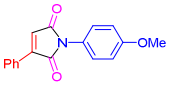
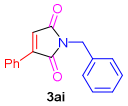
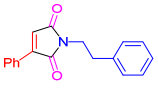
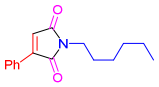
13	 1m	 3ma	82
14	 1n	 3na	71

[a]Reaction conditions: 1 (1.5 mmol), 2 (1.0 mmol), $PdCl_2$ (2.0 mol%), CO (15 bar), air (5 bar), toluene (2.0 mL), 120 °C, 12 h.

Table 2 Pd-catalyzed oxidative aminocarbonylation of alkynes: Variation of amines.[a]



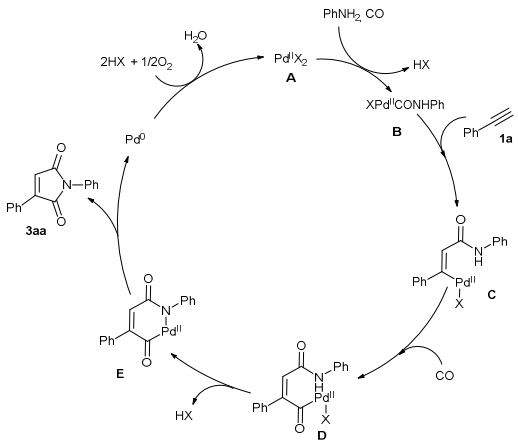
1a 2b-2l 3ab-3al

Entry	Amines	Product	Yield/%
1	 2b	 3ab	91
2	 2c	 3ac	84
3	 2d	 3ad	81
4	 2e	 3ae	95
5	 2f	 3af	91
6	 2g	 3ag	78
7	 2h	 3ah	71
8	 2i	 3ai	91
9	 2j	 3aj	87
10[b]	 2k	 3ak	76
11	 2l	 3al	84

[a]Reaction conditions: 1 (1.5 mmol), 2 (1.0 mmol), $PdCl_2$ (2.0 mol%), CO (15 bar), air (5 bar), toluene (2.0 mL), 120 °C, 12 h. [b] Methylamine solution, 2.0 M in THF, 1.0 mmol.

Aromatic amines bearing chloro- or bromo-atoms on the phenyl ring **(2c, 2d)**, which are often sensitive to palladium catalysis, also worked well, without adverse effect on the reaction. At the same time, the steric hindrance of the substituent on the amine also has a certain influence on the reaction, the yield of 2-methylaniline **(2g)** is moderately lower than that of unsubstituted aniline. Bioactive amines **(2i, 2j)** yielded the corresponding products in 87-91%. Similarly, for aliphatic amines **(2k, 2l)** this transformation gave the corresponding products in high yields (76-84%).

With respect to the mechanism it is interesting to note that the groups of Gabriele,[14] Xia,[15] and Muldoon[11c] reported related carbonylations to 2-ynamides in the presence of halide additives. However, under our conditions, the corresponding ynamides were not observed by GC-MS as intermediates to a significant extent. Hence, on the basis of previous mechanistic studies for oxidative carbonylations,[16] we propose the following pathway for this transformation (Scheme 2). First, the palladium acyl complex **B** was generated from palladium (II) **A** in the presence of amine and CO. Subsequently, π-coordination of the carbon- carbon triple bond to the metal center, followed by the insertion of the alkyne into the palladium carbon bond, affords palladium intermediates **C**. Then, the palladium species **C** undergoes CO insertion to give the acyl palladium species **D**. Finally, the maleimide is eliminated through reductive elimination of intermediate **E** to give the palladium (0) which is oxidized to palladium (II) in the presence of air to finish the catalytic cycle.



Scheme 2 Proposed catalytic cycle.

In conclusion, we have developed a ligand-free palladium catalyzed oxidative carbonylation of alkynes with amines to give poly-substituted maleimides in good to high yields (63-

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95%). In this convenient protocol air was utilized as the terminal oxidant without other co-oxidants.[17]

Notes and references

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