Heterogeneous & Homogeneous & Bio- & Nano-
CHEMCATCHEM
CATALYSIS

Accepted Article

Title: An Efficient Rhodium-Catalyzed Carbonylative Annulation of Internal Alkynes and Anilines to Produce Maleimides

Authors: Xiao-Feng Wu, Fengxiang Zhu, Yahui li, and Zechao Wang

To be cited as: *ChemCatChem* 10.1002/cctc.201601092

Link to VoR: http://dx.doi.org/10.1002/cctc.201601092

A Journal of
ChemPubSoc Europe

WILEY-VCH

www.chemcatchem.org

10.1002/cctc.201601092

WILEY-VCH

An Efficient Rhodium-Catalyzed Carbonylative Annulation of Internal Alkynes and Anilines to Produce Maleimides

Fengxiang Zhu,[a] Yahui Li,[a] Zechao Wang,[a] and Xiao-Feng Wu*[a]

Abstract: A selective and efficient procedure on carbonylative synthesis of polysubstituted maleimides has been developed. With rhodium as the catalyst and acetylaceton as the ligand, various desired maleimide derivatives were isolated in moderate to excellent yields with good functional group tolerance from the corresponding internal alkynes and anilines.

Approximately more than 70% of all pharmaceuticals and agrochemicals bearing at least one heterocyclic ring, which can be explained by two reasons: 1) the synthetic accessibility of heterocyclic scaffolds and its physicochemical properties, driving these values of lipophilicity and solubility toward the optimal balanced range regarding uptake and bioavailability; 2) heterocycles seem to be perfect bioisosteres of other iso- or heterocyclic rings as well as of several different functional groups which delivering through their similarity in structural shape and electronic distribution equal or even better biological efficacy. Hence, the development of new synthetic procedures for heterocycles synthesis is still considered as the core interest of organic chemists.[1] Among all the heterocyclic compounds, maleimide derivatives is an important class of heterocycles which have been widely used in pharmaceutical engineering,[2] natural rubbers,[3] resins[4] and aerospace industry (Figure 1).[5] Except these applications, *N*-arylmaleimide products due to their excellent heat resistance have also been applied in the engineering plastics.[6] Typically, maleimides can be prepared from maleic anhydride by treatment with amines followed by dehydration. Although numbers of alternative procedures have been developed, new synthetic methodologies are still under demand.[7]

On the other hand, carbon monoxide is one of the cheapest and most abundant C1 source. By transition metal-catalyzed carbonylative transformations, CO can be easily incorporated into the parent molecules and contribute to increase the diversity of accessible compounds in many ways. Due to the high synthetic values and academic interests, numerous novel carbonylation procedures have been established and even industrialized during the past decades.[8] And the combination of carbonylation and heterocycles synthesis is attractive as well.[9] High valued heterocycles can be prepared with cheap CO as one of the reactants. Indeed, carbonylation procedures have been reported for the synthesis of maleimide derivatives. In 2006, Kondo and co-workers reported an interesting ruthenium-catalyzed cocyclization of alkynes, isocyanates and CO for the synthesis of polysubstituted maleimides.[10a] Unsymmetrical maleimides can be prepared in excellent yields in a rapid and atom-economical manner (Scheme 1, eq. 1). Later on, $Fe(CO)_5$ was found to be a proper catalyst for this transformation as well.[10b] A rhodium-catalyzed carbonylation of alkynes with pyridin-2-ylmethylamine for the synthesis of maleimides was developed by Chatani's group.[11] Two molecules of CO were incorporated into the final products and the coordination of the pyridine nitrogen to the rhodium center was found to be essential for the success of this reaction (Scheme 1, eq. 2). Recently, Beller and co-workers reported a novel procedure on iron-catalyzed cyclization of alkynes with CO to succinimides.[12] Under their reaction conditions, when diphenylacetylene and cyclohexylamine or benzylamine were applied as the substrates, *N*-substituted maleinimides were formed (Scheme 1, eq. 3).

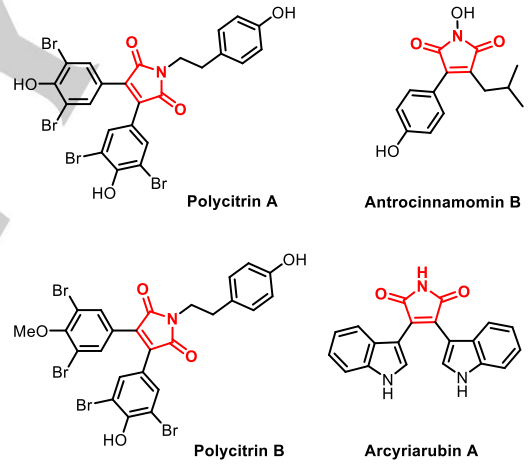


Figure 1. Selected examples of bio-active maleimides.

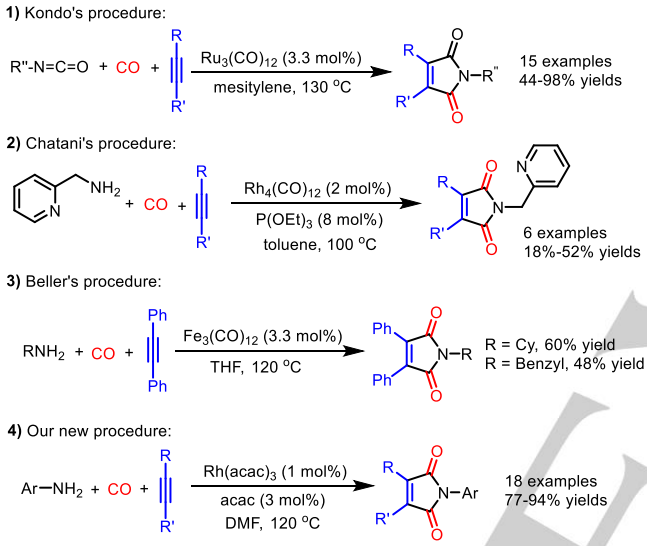
With all above discussed backgrounds and our continual interests in carbonylative synthesis of heterocycles, here we wish to report our new results on rhodium-catalyzed carbonylative synthesis of polysubstituted maleimides (Scheme 1, eq. 4). With readily available anilines and internal alkynes as the substrates, the desired products were isolated in good yields in general.

Initially, we choosing aniline and hex-3-yne as the model substrates in toluene, different rhodium catalysts were tested (Table 1, entries 1-5). As shown in Table 1, no desired 3,4-diethyl-1-phenyl-1*H*-pyrrole-2,5-dione could be detected with $[Rh(COD)Cl]_2$, $[Rh(OAc)_2]_2$, or $[Cp^*RhCl_2]_2$ as the catalyst (Table 1, entries1-3). To our delight, 21% and 31% of the desired product can be obtained in the presence of Rh(acac)(COD) or $Rh(acac)_3$ as the catalyst (Table 1, entries 4-5). With this exciting primary reactivity results in hand, we started the ligands

[a] F. Zhu, Y. Li, Z. Wang, Prof. Dr. X.-F. Wu
Leibniz-Institut für Katalyse e.V. an der Universität Rostock,
Albert-Einstein-Strasse 29a, 18059 Rostock (Germany)
E-mail: Xiao-Feng.Wu@catalysis.de

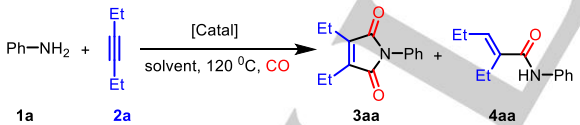
Supporting information for this article is given via a link at the end of the document.

effects testing which have been known hold strong influences on transition-catalyzed carbonylation reactions (Table 1, entries 6-9).[13] Among all the tested ligands, acetylaceton gave the best conversion of starting materials and 71% yield of the desired product can be observed (Table 1, entry 9). In the case of phosphine ligands, 20-30% of the corresponding *α,β*-unsaturated amides can be detected (Table 1, entries 6-8). Nitrogen ligands such as 1,10-phen. and bipyridine were found not effective here. Then, the effects of the solvents were checked with acetylaceton as the ligand (Table 1, entries 10-13). Interestingly, 95% of yield can be achieved with DMF as the media (Table 1, entry 13). However, the reaction was totally inhibited in DMSO (Table 1, entry 11). Notably, the same results can be obtained with 1% of $Rh(acac)_3$ and the loading can even be as low as 0.5 mol% (Table 1, entries 14 and 15).



Scheme 1. Transition metal-catalyzed carbonylative synthesis of maleimides.

Table 1. Optimization of the Reaction Conditions.[a]



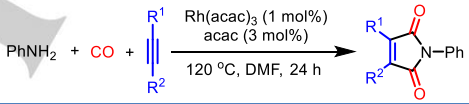
1a 2a 3aa 4aa

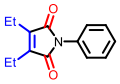
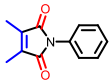
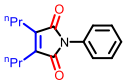
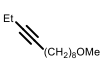
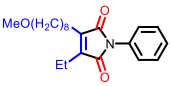
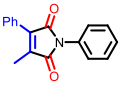
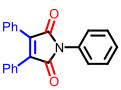
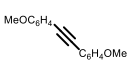
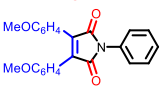
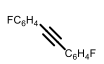
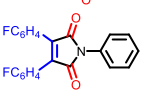
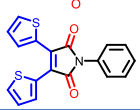
Entry	[Catal]	Ligand	Solvent	Yield(%)[b]
1	$[Rh(COD)Cl]_2$	-	Toluene	-
2	$[Rh(OAc)_2]_2$	-	Toluene	-
3	$[Cp^*RhCl_2]_2$	-	Toluene	-
4	$Rh(acac)_3$	-	Toluene	31
5	RhCOD(acac)	-	Toluene	21
6	$Rh(acac)_3$	PPh_3	Toluene	21
7	$Rh(acac)_3$	DPPP	Toluene	18
8	$Rh(acac)_3$	DPEPhos	Toluene	25
9	$Rh(acac)_3$	acac	Toluene	71
10	$Rh(acac)_3$	acac	CH_3CN	80
11	$Rh(acac)_3$	acac	DMSO	-
12	$Rh(acac)_3$	acac	THF	43
13	$Rh(acac)_3$	acac	DMF	95
14[c]	$Rh(acac)_3$	acac	DMF	94
15[d]	$Rh(acac)_3$	acac	DMF	87

[a] aniline (0.2 mmol), hex-3-yne (0.22 mmol), catalysis (2 mol%), PPh_3 (6 mol%), 120 °C, CO (10 bar), solvent (1 mL), 24h. [b] GC yields using hexadecane as the internal standard. [c] $Rh(acac)_3$ (1 mol%). [d] $Rh(acac)_3$ (0.5 mol%). PPh_3: triphenylphosphane; DPEphos: bis(2-diphenylphosphinophenyl)ether; DPPE: 1, 2-bis(diphenylphosphino)ethan; acac: acetylaceton; Cp*: pentamethylcyclopentadienyl; COD: 1,5-cyclooctadiene.

With the best reaction conditions in hand, we started the limitation and generality testing of this new procedure (Tables 2 and 3). Under our standard reaction conditions, good to excellent yields of phenyl-1*H*-pyrrole-2,5-diones can be produced from aniline and the corresponding internal alkynes (Table 2). Diaryl acetylenes with electron-donating or electron-withdrawing substituents are all shown to be suitable substrates here, and give the desired maleimides in good yields (Table 2, entries 6-9). It is important to mention that terminal alkynes (phenylacetylene, ethynylcyclohexane, hex-1-yne) were tested with aniline under our conditions as well, but no wished products can be detected.

Table 2. Rh-catalyzed carbonylative synthesis of maleimides: Substrate scope of alkynes.[a]

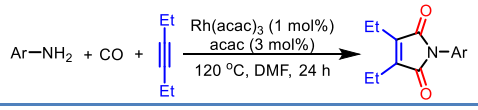


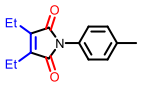
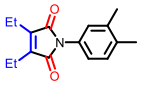
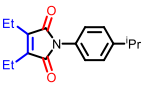
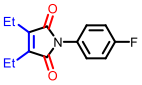
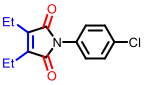
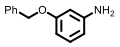
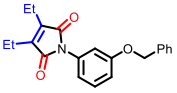
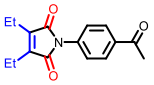
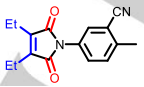
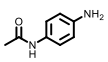
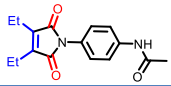
Entry	Alkyne	Product	Yield (%)
1			93
2			94
3			81
4			89
5			84
6			86
7			87
8			81
9			77

[a] aniline (0.2 mmol), alkynes (0.22 mmol), $Rh(acac)_3$ (1 mol%), acetylaceton (3 mol%), 120 °C, CO (10 bar), DMF (1 mL), 24 h, isolated yield.

Subsequently, different anilines were tested with hex-3-yne as the model substrate (Table 3). Anilines with electron-donating or electron-withdrawing functional groups are all suitable substrates for this methodology. Good to excellent yields can be achieved in all the tested cases. However, aliphatic amines cannot be applied here instead of aniline.

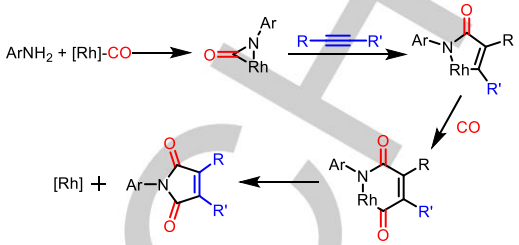
Table 3. Rh-catalyzed carbonylative synthesis of maleimides: Substrate scope of anilines.[a]



Entry	Aniline	Product	Yield (%)
1			91
2			84
3			87
4			83
5			89
6			83
7			86
8			77
9			86

[a] anilines (0.2 mmol), alkyne (0.22 mmol), $Rh(acac)_3$ (1 mol%), acetylaceton (3 mol%), 120 °C, CO (10 bar), DMF (1 mL), 24 h, isolated yield.

Based on our results, a possible reaction is proposed (Scheme 2). At the beginning, the real rhodium catalyst was generated from the precursor in the presence of ligand and CO. Then the generated rhodium catalyst reacted with aniline to give the corresponding three-membered rhodium cycle which subsequently reacted with internal alkynes to the desired five-membered cycle. A six-membered cycle as one of the key intermediates will be formed after the insertion of another molecular of CO. Finally, the final maleimides were eliminated through reductive elimination and complete he catalytic cycle.



Scheme 2. Proposed reaction pathway.

In conclusion, an efficient rhodium-catalyzed carbonylative annulation of anilines with internal alkynes for the straightforward synthesis of maleimide derivatives has been developed. With rhodium as the catalyst and acetylaceton as the ligand, various polysubstituted maleimides were isolated with high yields.

Acknowledgements

The authors thank the Chinese Scholarship Council for financial support. We also appreciate the general supports from Professor Matthias Beller and the help from Mr. Jie Liu both in LIKAT. The analytic supports of Dr. W. Baumann, Dr. C. Fisher, S. Buchholz, and S. Schareina are gratefully acknowledged.

General procedure: Under an open atmosphere or under argon, a 4 mL screw-cap vial was charged with $Rh(acac)_3$ (1 mol%), acetylaceton (3 mol%), aniline (0.2 mmol), alkyne (0.22 mmol), dry DMF (1 mL) and an oven-dried stirring bar. The vial was closed by Teflon septum and phenolic cap and connected with atmosphere with a needle. Then the vial was fixed in an alloy plate and put into Paar 4560 series autoclave (300 mL). At room temperature, the autoclave is flushed with carbon monoxide for three times and 10 bar of carbon monoxide was charged. The autoclave was placed on a heating plate equipped with magnetic stirring and an aluminum block. The reaction is allowed to be heated under 120 °C for 24 hours. Afterwards, the autoclave was cooled to room temperature and the pressure was carefully released. The reaction solution was quenched with distilled water and extracted with ethyl acetate three times. The combined organic phases were washed with saturated NaCl solution and dried over Na_2SO_4. The crude product was purified by column chromatography (ethyl acetate/pentante = 1:30) to give the pure product.

Keywords: domino reaction • carbonylation • maleimides • annulation • heterocycle synthesis

[1] a) J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, *Modern Heterocyclic Chemistry*, Wiley-VCH, **2011**; b) J. A. Joule, K. Mills, *Heterocyclic Chemistry*, Wiley-Blackwell, Oxford, **2010**; c) L. D. Quin, J. Tyrell, *Fundamentals of Heterocyclic Chemistry*, Wiley-Blackwell, Oxford,

2010; d) A. R. Katritzky, C. A. Ramsden, J. A. Joule, V. V. Zhdankin, *Handbook of Heterocyclic Chemistry*, Elsevier, Amsterdam, **2010**; e) R. K. Bansal, *Heterocyclic Chemistry*, Anshan, Tunbridge Wells, **2008**; f) T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles*, Wiley-VCH, **2003**; g) J. Dinges, C. Lamberth, *Bioactive Heterocyclic Compound Classes: Pharmaceuticals*, Wiley-VCH, **2012**.

[2] a) N. Matuszak, G. G. Muccioli, D. M. Lambert, *J. Med. Chem*. **2009**, *52*, 7410-7420; b) J. T. Ferrara, L. M. Cano, M. E. Fonseca, *Bioorg. Med. Chem. Lett.* **2003**, *3*, 1825-1827; c) A. Warnecke, I. Fichtner, F. Kratz, *Bioconjugate Chem*. **2004**, *15*, 1349-1359; d) C. Peifer, T. Stoiber, G. Dannhardt, *J. Med. Chem*. **2006**, *49*, 1271-1281; e) S. Peukert, J. Brendel, H. Hemmerle, *Bioorg. Med. Chem. Lett*. **2004**, *14*, 2823-2827.

[3] a) J. C Basurto, I. V. Alcántara, J. G. T. Ferrara, Eur. *J. Med. Chem.* **2005**, *40*, 732-735; b) R. Patel, S. A. Sabet, US Patent 5621045, **1997**.

[4] A. Switky, US Patent 2413489, **1995**.

[5] J. P. Huang, E. N. Whman, US Patent 2010218892, **2010**.

[6] a) D. Barry, European Patent 0234766, **1995**; b) T. D. Traugott, L. Workentine, US Patent 5412036, **1995**; c) T. Shinmura, K. Konishi, US Patent 5532317, **1996**.

[7] For selected examples, see: a) L. Bouissane, J. P. Sestelo, L. A. Sarandeses, *Org. Lett.* **2009**, *11*, 1285-1288; b) M. Ambrogi, A. Ciogli, M. Mancinelli, S. Ranieri, A. Mazzanti, *J. Org. Chem.* **2013**, *78*, 3709-3719; c) P. S. Deore, N. P. Argade, *J. Org. Chem.* **2012**, *77*, 739-746; d) F. Mangin, E. Banaszak-Léonard, C. Len, *RSC Adv.* **2015**, *5*, 69616-69620; e) L. H. Lim, J. Zhou, *Org. Chem. Front.* **2015**, *2*, 775-777.

[8] a) L. Kollär, *Modern Carbonylation Methods*; Wiley-VCH, **2008**; b) X.-F. Wu, H. Neumann, *ChemCatChem* **2012**, *4*, 447-458; c) X.-F. Wu, H. Neumann, M. Beller, *ChemSusChem* **2013**, *6*, 229-241; d) X.-F. Wu, H. X. Fang, L. Wu, R. Jackstell Neumann, M. Beller, *Acc. Chem. Res*. **2014**, *47*, 1041-1053; e) R. Skoda-Foldes and L. Kollör, *Curr. Org. Chem*. **2002**, *6*, 1097-1119; f) B. Gabriele, R. Mancuso, G. Salerno, *Eur. J Org. Chem.* **2012**, 6825-6839; g) S. D. Friis, A. T. Lindhardt, T. Skrydstrup, *Acc. Chem. Res*. **2016**, *49*, 594-605; h) X.-F. Wu, *RSC Adv.* **2016**, *6*, 83831-83837.

[9] X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev*. **2013**, *113*, 1-35.

[10] a) T. Kondo, M. Nomura, Y. Ura, K. Wada, T. Mitsudo *J. Am. Chem. Soc.* **2006**, *128*, 14816-14817; b) P. Mathur, R. K. Joshi, D. K. Rai, B. Jha, S. M. Mobin, *Dalton Trans.* **2012**, *41*, 5045-5054.

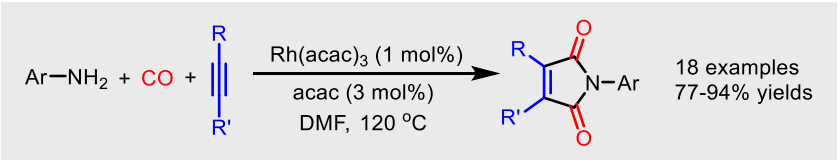
[11] S. Inoue, Y. Fukumoto, N. Chatani, *J. Org. Chem.* **2007**, *72*, 6588-6590.

[12] a) K. M. Driller, H. Klein, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 6041-6044; b) S. Prateeptongkum, K. M. Driller, R. Jackstell, A. Spannenberg, M. Beller, *Chem. Eur. J.* **2010**, *16*, 9606-9615; c) S. Prateeptongkum, K. M. Driller, R. Jackstell, M. Beller, *Chem. Asian J.* **2010**, *5*, 2173-2176.

[13] C. A. Tolman, *Chem. Rev.* **1977**, *77*, 313-348.

10.1002/cctc.201601092

COMMUNICATION



A selective and efficient procedure on carbonylative synthesis of polysubstituted maleimides has been developed. With rhodium as the catalyst and acetylaceton as the ligand, various desired maleimide derivatives were isolated in moderate to excellent yields.

*Fengxiang Zhu,Yahui Li, Zechao Wang, and Xiao-Feng Wu**

Page No. – Page No.

An Efficient Rhodium-Catalyzed Carbonylative Annulation of Internal Alkynes and Anilines to Produce Maleimides