

An assessment of late transition metals as hydroamination catalysts in the cyclization of C-propargyl vinylogous amides into pyrroles

Allan M. Prior, Ross S. Robinson*

Warren Research Laboratory, School of Chemistry, University of KwaZulu-Natal, Corner of Golf and Ridge Roads, Private Bag X01, Scottsville, Pietermaritzburg 3209, South Africa

Received 21 August 2007; revised 12 November 2007; accepted 21 November 2007

Available online 24 November 2007

Abstract

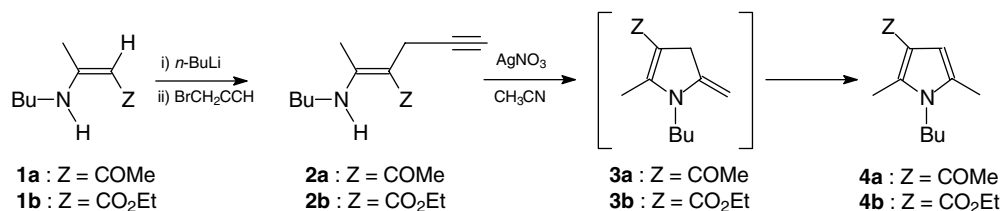
It has been shown that common and inexpensive salts of the late transition metals serve as effective hydroamination catalysts in the conversion of C-propargyl vinylogous amides into pyrroles. The oxide, acetate, nitrate and chloride derivatives of Cu(II), Ag(I), Zn(II), Cd(II) and Hg(II) were utilized as hydroamination catalysts in the oxidation states shown. Although the Zn(II) catalysts with the exception of ZnO afforded the highest yields of product under mild conditions, all of the group 12 metal catalysts provided excellent yields of product under more forcing conditions. The nature of the counterion plays an important role in the efficiency of hydroamination reactions, as well as the Lewis acidity of the metal centre.

© 2007 Elsevier Ltd. All rights reserved.

The construction of C–N bonds is an important and often challenging synthetic step, which validates the continued research into alternative catalytic approaches towards their formation.¹ The inter- or intramolecular addition of secondary amines, primary amines or ammonia to double and triple bonds, namely, hydroamination, has attracted a great deal of attention in organic synthesis due to its ability and versatility in forming such bonds.² Howk et al. in 1954 showed that primary amines and ammonia could be added to alkenes in the presence of an alkali metal or its hydride, however, high temperatures and pressures were

required to bring about such reactions.³ More recently, milder reaction conditions employing catalysts based on early transition metals, groups 3–5,^{4–6} late transition metals, groups 9–12⁷ as well as early lanthanides⁸ and actinides⁹ have been reported.

Dovey et al. recently published a novel synthetic approach towards the preparation of functionalized pyrroles **4a** (Z = COMe) via the C-propargylation of vinylogous amides **1a** followed by intramolecular hydroamination of the C-propargyl vinylogous amides **2a** (Scheme 1).¹⁰ The hydroamination reaction proceeds via



Scheme 1.

* Corresponding author. Tel.: +27 33 260 6272; fax: +27 33 260 5009.
E-mail address: robinsonr@ukzn.ac.za (R.S. Robinson).

the cyclic enamine intermediate **3a** in the presence of a catalytic amount (0.2 equiv) of silver nitrate in acetonitrile at room temperature to afford product **4a** in 95% yield typically after 16–20 h.¹⁰

Reported herein is a catalytic study assessing the efficacy of late transition metals in facilitating the cyclization of **2b** ($Z = \text{CO}_2\text{Et}$) into the corresponding pyrrole **4b** under microwave conditions, and in addition, an investigation of the influence of various counterions. It is advantageous to employ the ester functionality due to its ability and versatility in being subsequently transformed into a wide array of functional groups.¹¹ The ester functionality may alternatively be converted into a carboxylic acid and subsequently removed via decarboxylation.¹² The oxide, acetate, nitrate and chloride, derivatives of group 11 and 12 metals, namely, Cu(II), Ag(I), Zn(II), Cd(II) and Hg(II) were chosen as potential hydroamination catalysts in the oxidation states provided. To perform the study we were in need of a synthetic route to access *C*-propargyl vinyllogous amides of the type ($Z = \text{CO}_2\text{Et}$) **2b**.

In our hands we were able to facilitate this reaction via the direct *C*-propargylation of the vinyllogous amide **1b** ($Z = \text{CO}_2\text{Et}$) to afford product **2b** in 80% yield as determined by ¹H NMR spectroscopy.¹³ This result is in contrast to the report by Dovey et al.,¹⁰ in which the *C*-propargyl vinyllogous amides of type **2b** were not successfully synthesized. The *cis*-configuration about the double bond was preserved during the *C*-propargylation reaction due to hydrogen bonding between the amine N–H and the carbonyl oxygen. This was evident from the

downfield shift of the N–H signals in the ¹H NMR spectra, and by NOE experiments.¹⁰

With the *C*-propargyl vinyllogous amides in hand we set about carrying out the microwave assisted hydroamination study utilizing each transition metal at a catalytic loading of 0.04 equiv in acetonitrile (Table 1).¹⁴ Interestingly, all transformations were completely regioselective, yielding exclusively Markovnikov addition type products. These products resulted from the *C*-propargyl vinyllogous amides undergoing 5-*exo*-dig cyclizations affording aromatic, 5-membered pyrroles, as opposed to 6-*endo*-dig cyclizations, to form non-aromatic, 6-membered heterocycles.¹⁵

Due to the C–C triple bond being *trans* relative to the amine in the starting material **2b**, isomerization about the enamine double bond must initially take place, allowing for the amine to approach the activated C–C triple bond, thus initiating hydroamination. In the absence of a metal catalyst, no geometrical isomerization was evident. It is known that geometrical isomerization about double bonds may be facilitated by the presence of a metal catalyst,¹⁷ which could account for the geometrical isomerization observed in our reactions. This isomerization can be attributed to the fact that a metal–olefin complex may exist in equilibrium with a polarized form allowing for rotation about the temporarily polarized double bond (Scheme 2).¹⁸

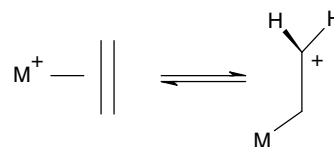
It is apparent from entry a that the absence of a catalyst greatly hinders the hydroamination of **2b** into the cyclized product **4b**. It has been suggested that when the nitrogen lone pair from the amine approaches the π -bond of the electron-rich olefin in the absence of any catalyst, the electrostatic repulsions that result tend to cause high activation energies leading to particularly low reaction rates.¹⁹ When a metal catalyst was introduced, a significant increase in reaction rate was noticed with the exception of ZnO, which afforded a 3% yield of pyrrole **4b**. The poor catalytic activity of ZnO as a hydroamination catalyst remains consistent with the literature and is a result of its low Lewis acidity.^{20,21}

Whilst assessing the group 11 metals as hydroamination catalysts, it was noticed that the Cu²⁺ catalysts, that is, CuO, CuAc₂, Cu(NO₃)₂ and CuCl₂ were generally superior in contrast to the corresponding Ag⁺ catalysts in facilitating hydroamination. Group 12 metals showed similar trends in catalytic activity, with a general decrease in catalytic activity down the periodic group from Zn²⁺ to Hg²⁺. It was also noted that the nature of the counterion had a marked effect on the catalytic activity of a metal in performing hydroamination. The observed catalytic activity

Table 1
Hydroamination of vinyllogous amide **2b** to pyrrole **4b**, implementing numerous transition metal catalysts^a

Entry	Catalyst	Yield 4b (%)
a	None	3
b	CuO	13
c	CuAc ₂	33
d	Cu(NO ₃) ₂	53
e	CuCl ₂	65
f	Ag ₂ O	6
g	AgAc	7
h	Ag(NO ₃)	14
i	AgCl	9
j	ZnO	3
k	ZnAc ₂	96
l	Zn(NO ₃) ₂	99
m	ZnCl ₂	93
n	CdO	39
o	CdAc ₂	30
p	Cd(NO ₃) ₂	85
q	CdCl ₂	72
r	HgO	24
s	HgAc ₂	68
t	Hg(NO ₃) ₂	57
u	HgCl ₂	36
v	ZnI ₂	14
w	HgI ₂	94

^a Under more forcing reaction conditions, the catalysts in entries k–u yielded pyrrole **4b** in a $\geq 96\%$ yield.¹⁶



Scheme 2.

of a particular metal within a series generally increased in the order of oxide < acetate < chloride < nitrate.

Burling et al. similarly showed that the nature of the counterion can indeed play a role in the rate of hydroamination reactions.²² Burling observed that bulkier and less coordinating anions tended to increase the rate of reactions, however, if too non-coordinating, a paradoxical drop off in reaction rate can result due to instability of the catalyst in solution.

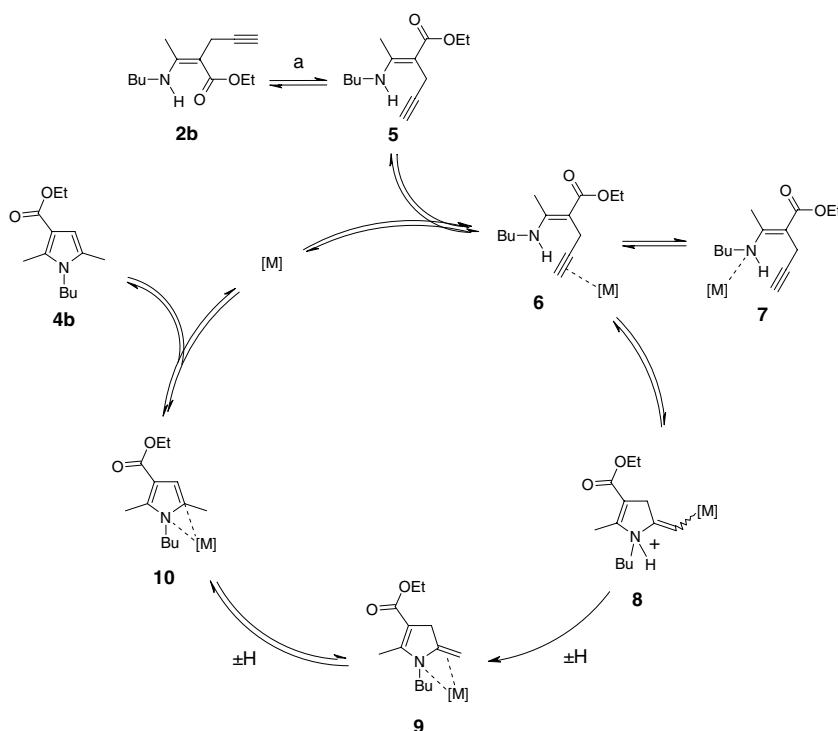
As mentioned earlier, the activities of the catalysts employed generally decreased down the periodic groups, from Zn^{2+} to Hg^{2+} , and from Cu^{2+} to Ag^+ , respectively. In an attempt to account for the observed trends in activity, the stability of metal complexes based upon hard soft acid base theory (HSAB) was considered. It is well known that the stability of Hg^{2+} (soft metal Lewis acid) halide complexes decrease in the order $I > Br > Cl > F$ but with harder, more electropositive metal Lewis acids, the reverse order applies.²³ Looking at the chloride catalysts of group 12 as an example, the yield decreased from 93% ($ZnCl_2$ entry m), to 72% ($CdCl_2$ entry q), and finally to 36% ($HgCl_2$ entry u). To assess whether increasing catalyst instability was a potential cause for the reduced activity from $ZnCl_2$ to $HgCl_2$, a softer counterion was employed in the hope of reversing catalyst stabilities. ZnI_2 and HgI_2 were subsequently employed as potential hydroamination catalysts (entries v and w) with the expectation that the soft–soft interactions in HgI_2 would result in a more stable complex in solution, as opposed to the harder–soft

interactions in ZnI_2 . As expected, the yield of **4b** decreased from 93% ($ZnCl_2$ entry m) to 14% (ZnI_2 entry v), and increased from 36% ($HgCl_2$ entry u) to 94% (HgI_2 entry w) suggesting that reduced activities may be attributed to the counterions being too non-coordinating, as described by Burling.

Furthermore, the observed trend in catalytic activities down a periodic group may be attributed to the progressive decrease in Lewis acidity of the cationic metal centres, resulting from decreasing charge to radius ratios in moving down a group.²⁴ The Lewis acidity of a catalyst plays an important role in hydroamination for the reason that if the Lewis acidity of the metal cation is too weak, poor activation of the triple bond may result, leading to lower reaction rates.²¹

A generally accepted catalytic cycle adapted from Muller et al. is depicted in Scheme 3.²⁵ Despite the number of catalytic hydroamination mechanisms known, such as amine activation²⁶ or oxidative addition,²⁷ the following mechanism may be used to rationalize a Lewis acid catalyzed hydroamination process. The C–C triple bond initially becomes activated through π -coordination to the metal centre of the catalyst, followed by nucleophilic attack of the nitrogen lone pair on the activated triple bond.²⁵

This is in contrast to the mechanism based on oxidative addition of an amine to the metal centre, which cannot explain $Zn(II)$ and $Cu(I)$ catalyzed hydroamination reactions, as these metals have no oxidation states available for the donation of two more electrons.²⁵ It is unlikely that



Scheme 3. Metal catalyzed isomerization adapted from Muller et al. Note: Formal [1,3]-hydrogen shifts are depicted by $\pm H$.

an amine activation type mechanism will exist in this case as none of the catalysts employed in this study are basic enough for amino proton extraction.²⁸

In conclusion, it can be seen that metals of the late transition series can indeed serve as efficient and regioselective catalysts in facilitating the hydroamination of functionalized *C*-propargyl vinylogous carbamates into pyrroles. Advantages lie in the fact that these metal salts are commonly available, inexpensive and stable to air and moisture. The zinc catalysts with the exception of ZnO gave the highest yields under mild conditions, however, all the group 12 metals afforded excellent yields of product when longer reaction times, higher catalytic loading and increased microwave energy were utilized. The stability of the catalysts in solution, as well as the Lewis acidity of the catalysts, plays an important role in the efficiency of hydroamination reactions. Changing the counterion had a noticeable effect on hydroamination, and it has been suggested that less coordinating anions result in higher rates up to a point at which catalyst stability in solution becomes compromised as a result of anions becoming too non-coordinating.

Acknowledgements

The authors would like to acknowledge The National Research Foundation for providing generous funding, as well as Mr. Craig Grimmer for acquiring ¹H NMR data.

References and notes

- (a) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609–3612; (b) Ma, D.; Yao, J. *Tetrahedron: Asymmetry* **1996**, *7*, 3075–3078; (c) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217–7218; (d) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216; (e) Robinson, R. S.; Dovey, M. C.; Gravestock, D. *Eur. J. Org. Chem.* **2005**, *3*, 505–511; (f) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264–1267; (g) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268–1273.
- Nobis, M.; Driebßen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983–3985.
- Howk, B. W.; Little, E. L.; Scott, S. L.; Whitman, G. M. *J. Am. Chem. Soc.* **1954**, *76*, 1899–1902.
- Bambirra, S.; Tsurugi, H.; van Leusen, D.; Hessen, B. *Dalton Trans.* **2006**, 1157–1161.
- Anderson, L. L.; Arnold, J.; Bergman, R. G. *Org. Lett.* **2004**, *6*, 2519–2522.
- Lorber, C.; Choukroun, R.; Vendier, L. *Organometallics* **2004**, *23*, 1845–1850.
- Müller, T. E.; Pleier, A.-K. *J. Chem. Soc., Dalton Trans.* **1999**, 583–587.
- Kim, Y. K.; Livinghouse, T.; Bercaw, J. E. *Tetrahedron Lett.* **2001**, *42*, 2933–2935.
- Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407–1420.
- Robinson, R. S.; Dovey, M. C.; Gravestock, D. *Tetrahedron Lett.* **2004**, *45*, 6787–6789.
- Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; VHC, 1989. pp 981–988.
- Stahly, G. P.; Marlett, E. M.; Nelson, G. E. *J. Org. Chem.* **1983**, *48*, 4423–4426.
- 2.0 M *n*-BuLi (2.97 mL; 5.94 mmol) was added dropwise to a stirred solution of vinylogous amide (1.00 g; 5.40 mmol) in dry THF (50 mL) at 0 °C. The solution was stirred for 30 min at 0 °C followed by an additional 30 min of stirring at room temperature. The solution was cooled to 0 °C followed by the dropwise addition of propargyl bromide (0.814 g; 6.48 mmol). The solution was stirred at 0 °C for 30 min, allowed to warm to room temperature, and stirred for an additional 14 h. The reaction mixture was quenched with 2 M NH₄Cl (five drops) and concentrated in vacuo to yield the crude *C*-propargyl vinylogous amide as a brown oil, in 80% yield.
- Transition metal salt (0.0358 mmol, 0.04 equiv) was added to a solution of crude *C*-propargyl vinylogous amide (200 mg, 0.896 mmol) and acetonitrile (2 mL) in a microwave reaction vessel, and subjected to 40 W of microwave irradiation for 20 s whilst being stirred and force cooled. The reaction mixture was purified with a short silica plug (1 cm) and analyzed using ¹H NMR spectroscopy. All microwave reactions were performed using a CEM Discover laboratory microwave oven.
- (a) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846–3852; (b) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.
- Refer to Ref. 14 with the exception that 0.2 equiv of catalyst, 100 W of microwave irradiation, and a reaction time of 1 min were utilized.
- Field, L. D.; Ward, A. J. *J. Organomet. Chem.* **2003**, *681*, 91–97.
- Bochmann, M. *Organometallics 2: Complexes with Transition Metal–Carbon π-Bonds*; Oxford University Press, 2000; pp 20–21.
- Hultsch, K. C. *Org. Biomol. Chem.* **2005**, *3*, 1819–1824.
- Penzién, J.; Müller, T. E.; Lercher, J. A. *Chem. Commun.* **2000**, 1753–1754.
- Shanbhag, G. V.; Halligudi, S. B. *J. Mol. Catal. A: Chem.* **2004**, *222*, 223–228.
- Burling, S.; Field, L. D.; Messerle, B. A.; Turner, P. *Organometallics* **2004**, *23*, 1714–1721.
- Bodie, D.; McDaniel, D.; Alexander, J. *Concepts and Models of Inorganic Chemistry*, 3rd ed.; John Wiley Sons, 1994; pp 386–387.
- Pearson, R. G. *J. Chem. Educ.* **1968**, *45*, 581–587.
- Müller, T. E.; Grosche, M.; Herdtweck, E.; Pleier, A.-K.; Walter, E.; Yan, Y.-K. *Organometallics* **2000**, *19*, 170–183.
- Martinez, P. H.; Hultsch, K. I.; Hample, F. *Chem. Commun.* **2006**, 2221–2223.
- Uchamaru, Y. *Chem. Commun.* **1999**, 1133–1134.
- Ouh, L. L.; Müller, T. E.; Yan, Y. K. *J. Organomet. Chem.* **2005**, *690*, 3774–3782.