COMMUNICATIONS

Calcium-Catalyzed Cycloisomerization of Enynes

Vera J. Meyer,^a Liang Fu,^a Fabian Marquardt,^a and Meike Niggemann^{a,*}

^a Institute for Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany Fax: (+49)-241-8092-127; phone: (+49)-241-8094-688; e-mail: niggemann@oc.rwth-aachen.de

Received: March 28, 2013; Revised: May 14, 2013; Published online: July 12, 2013

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300253.

Abstract: A cycloisomerization of enynes with a benign calcium catalyst is presented exploring a complementary reactivity to that usually found in transition and noble metal-catalyzed reactions. Thereby, a systematic investigation of the π -activation of alkynes with reactive carbocations has been realized and ketones of various ring sizes were easily accessed. We are certain that these basic investigations will pave the way for the elaboration of further reactions based on the reaction principles discovered in the area of noble metal catalysis.

Keywords: calcium catalysis; cycloisomerization; enynes; noble metal catalysis; vinyl carbocations

The efficient introduction of scaffold diversity and complexity, while preferentially departing from simple and readily available starting materials in a minimum of chemical operations, is one of the most challenging missions of modern organic synthesis. Addressing this objective, the field of noble metal catalysis has witnessed a veritable boom within the last decade. Due to the peculiar abilities of noble metals as π -acids for carbophilic activation, a wide range of conceptually new reaction types has been discovered.^[1] Reactive intermediates in gold-catalyzed reactions have been described either as cationic or carbenoid species.^[2] In the cationic rendition, the initially formed reactive species is a gold-stabilized vinyl cation, generated by the attack of the gold catalyst onto the alkyne moiety. Skeletal rearrangements of this non-classical vinyl cation then account for the accessibility of a multitude of unusual frameworks such as vinylcyclopropanes or strained bridgehead cyclobutenes. One possibility to generate a similar reactivity is the activation of the alkyne moiety with one or more equivalents of electrophilic iodine sources, thus generating an analogous iodine-stabilized vinyl cation species.^[3] Even higher degrees of complexity from acyclic polyunsaturated precursors, also in the ab-



Figure 1. Outline for the π -activation of alkynes with reactive carbocations.

sence of any transition metal or stoichiometric reagent, might be achieved by the π -activation of alkynes with reactive carbocations (cf. Figure 1), thereby again generating a highly reactive vinyl cation that sets the stage for subsequent cycloisomerization reactions in analogy to the parent gold- and iodine-mediated reactions. We have recently demonstrated that skeletal rearrangements normally granted by noble metal bound non-classical cations can be highly prolific also in the absence of the metal.^[4] It has been demonstrated by some scattered literature precedents that the generation of a vinyl cation via attack of a carbocation onto a triple bond is indeed feasible.^[5] Nevertheless a systematic investigation of the observed reactivity is lacking despite its high value as a starting point for the rich follow-up chemistry that is conceivable.

As a new branch of sustainable metal catalysis, the application of early main group metals as an alternative to traditionally used, expensive, rare and often highly toxic transition metal catalysts has emerged within the last couple of years. Among the other early main group metals, calcium seems to be particularly privileged, which is reflected by a considerable intensification of research around the analysis of the nature of calcium complexes^[6] and the exploration of its potential as a catalyst.^[7] Taking part in these efforts, we have recently developed a novel calcium catalyst for organic synthesis.^[8] The choice of appropriate counter-anions allowed for a first successful application of calcium salts as highly efficient catalysts for the transformation of environmentally benign π -activated alcohols and olefins. Having thus in hand a new

© 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

WILEY CONLINE LIBRARY

These are not the final page numbers! **77**

Table 1. Optimization of the reaction conditions.



Entry ^[a]	Solvent	Additive	H ₂ O source (mol%)	Ratio 2:3	Yield [%] ^[b]
1	DCM	Bu_4NPF_6	-	0:100	50
2	toluene	Bu_4NPF_6	_	0:100	75
3	DCE	Bu_4NPF_6	_	0:100	50
4	MeNO ₂	Bu_4NPF_6	_	61:39	90
5	MeNO ₂	Bu_4NBF_4	_	77:23	76
6	MeNO ₂	Bu_4NSbF_6	_	59:41	86
7	$MeNO_2$	$Me_2PhNH \cdot B(C_6F_5)_4$	_	_	_
8	MeNO ₂	Bu ₄ NPF ₆	H ₂ O (100)	58:42	83
9	MeNO ₂	Bu_4NPF_6	$MgSO_4 \cdot xH_2O$ (100)	100:0	87
10	MeNO ₂	Bu_4NPF_6	$MgSO_4 \cdot x H_2O(10)$	100:0	88
11	MeNO ₂	Bu_4NPF_6	$MgSO_4 \cdot 7H_2O(10)$	60:40	85
12 ^[c]	MeNO ₂	HNTf ₂	_	59:41	89
13 ^[c]	MeNO ₂	$HNTf_{2}$, $Bu_{4}NPF_{6}$	_	40:60	68
14 ^[c]	MeNO ₂	HNTf ₂	$MgSO_4 \cdot x H_2O$ (100)	35:66	45
15 ^[c]	MeNO ₂	$HNTf_2$, Bu_4NPF_6	$MgSO_4 \cdot x H_2O(100)$	40:60	68

^[a] Additive, H_2O source and $Ca(NTf_2)_2$ were added at room temperature to enyne **1** (0.25 mmol) in 1.5 mL of solvent and stirred for 18 h at 50 °C.

^[b] Isolated yield.

^[c] In the absence of $Ca(NTf_2)_2$.

Lewis acidic catalyst, which provides access to reactive cationic intermediates from olefinic precursors with higher activity than most of the previously known catalysts, including transition metal-based Lewis acids, we envisaged a systematic investigation of the π -activation of alkynes with reactive carbocations.

A first model reaction has been designed according to the following considerations (see Figure 1). An olefin moiety in I serves as the carbocation precursor as we have demonstrated the high activity of the calcium catalyst for the transformation of this entity into reactive carbocations in previous publications.^[8b,d] To control the regioselectivity of the alkyne attack, the olefin in **I** is tethered to the alkyne moiety, thereby forcing the resulting vinyl cation in **III** into an exocyclic position, as its inclusion in a small to mediumsized ring is prohibited by sp-hybridization. In addition, the substituent R ought to be electron-rich, thus stabilizing an adjacent positive charge. The highly reactive vinyl cation **III** will be intercepted by a water molecule thus yielding the ketone IV via its corresponding enol. In addition to providing a systematic investigation of the π -activation of alkynes with reactive carbocations the envisioned study explores a reactivity that is complementary to the cycloisomerization reactions of enynes usually found in transition and noble metal catalysis.

Our studies began with the optimization of the reaction conditions for the cycloisomerization reaction of model compound 1 (see Table 1). In the presence of 5 mol% of Ca(NTf₂)₂ and 5 mol% of Bu₄NPF₆ in dichloromethane (entry 1) none of the desired product was detected even after prolonged reaction times, and only ketone 3 was formed in a moderate yield as a result of water addition after direct activation of the alkyne in 1 by the calcium catalyst. A change of solvent to nitromethane (entry 4) improved the results. In order to suppress the undesired background reaction to ketone 3 completely, different additives were screened (entries 5–7) and special emphasis was given to the amount of water that is present in the reaction mixture. The best results were obtained with the initial Bu₄NPF₆ additive in the presence of conventional, non-dried MgSO4·xH2O as a slowly releasing source of H₂O (entries 9–10). To ensure reproducibility of the results the solvent was partly dried via filtration through a pad of basic alumina, thereby adjusting a leveled content of residual water. Reaction of the model compound in the presence of $HNTf_2$ as the cat-

2

KK These are not the final page numbers!

rable 2. Cycloisonicitzation of 1,0-englies.						
{		5 mol% Ca(NTf ₂) ₂ /Bu ₄ NPF ₆				
R^2 R^1	<u> </u>	10 mol% MgSO ₄ ·x H ₂ O MeNO ₂ , 50 °C, 1 8h	$x \xrightarrow{R^2} R^3$			
Entry ^[a]	Product		Yield [%] ^[b]			
1	EtOOC EtOOC		85			
2	PhO ₂ S PhO ₂ S		72			
3	EtOOC EtOOC		66			
4	EtOOC EtOOC	о ————————————————————————————————————	71			
5	EtOOC EtOOC		72			
6	EtOOC EtOOC	0 CF ₃ 5f	60			
7	EtOOC EtOOC	o 5g	70			
8	EtOOC EtOOC	0 5h	72			
9	EtOOC EtOOC		60			
10	EtOOC EtOOC	o 5j	52			
11 12		0 5k/l	81 (5k , R=Me) 50 (5l , R=Ac)			

Table 2. Cycloisomerization of 1,6-enynes

[a] 10 mol% MgSO₄·H₂O, 5 mol% Bu₄NPF₆ and 5 mol% Ca(NTf₂)₂ were added at room temperature to enyne 4 (0.25 mmol) in 1.5 mL of MeNO₂ and stirred for 18 h at 50 °C.

^[b] Isolated yield.

Adv. Synth. Catal. 0000, 000, 0-0

© 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

alyst leads to a significant drop of both conversion and selectivity (entries 12–15). A simple protonation of the NTf₂⁻ anion, leading to what has recently been coined as a hidden Brønsted acid as the active catalytic species in the calcium-catalyzed reactions is thus unlikely.^[9] Nevertheless, as water is present in the reaction mixture, a partial or full hydration of the Ca²⁺ ion leading to the strong acidification of the coordinated water molecule cannot be ruled out, thereby generating a Lewis acid/Brønsted acid cooperative catalyst system providing different activity than either the Lewis acid or the Brønsted acid alone.

To showcase the scope of the reaction a series of different envnes was cyclized under the optimized reaction conditions (see Table 2 and Table 3). Different electronic properties of the arene moiety stabilizing the intermediary vinyl cation were found to be well tolerated. Other electron-donating groups than the methoxy substituent in model compound 1 such as the free hydroxy group in 4d or even the acid-labile OTBS moiety in 4c proved suitable. Cyclization precursors with a simple unsubstituted phenyl group (entry 1) as well as electron-withdrawing substituents, such as a chlorine atom (entry 5) and a CF₃ moiety (entry 6) reacted in good to excellent yields. Enynes with non- or alkyl-substituted alkynes were found to give complex reaction mixtures, presumably due to insufficient stabilization of the cationic charge of the reactive vinyl cation. Similar results were obtained when 1,2- and mono-substituted olefins were used as precursors for the formation of the initial carbocation.

The chemoselectivity of the reaction proved to be excellent. Highly reactive groups such as ketones and even aldehydes were found to interfere by no means with the desired reaction pathway (entries 7–9).

In a second series, 1,5- and 1,7-enynes were cyclized to ketones of different ring sizes (see Table 3). Once more, different electronic properties of the arene moiety were well tolerated and 5-membered rings were readily obtained (entries 1–3). Presumably due to the unfavourable ring size, the yields of 7-membered carbocycles from 1,7-enynes were found to be insufficient in the presence of 5 mol% of the calcium catalyst. Nevertheless, increasing the catalyst loading to 10 mol% delivered the desired products **7d** and **7e** in synthetically useful yields.

To exclude a mechanistic scenario involving the hydrolysis of the alkyne to the corresponding ketone (such as in 3) followed by an aldol-type addition to the carbocation, the ketone 8 was synthesized and submitted to the optimized reaction conditions (see Scheme 1).

The reaction proceeded cleanly to the cyclic olefin **9** in 76% yield, and no trace of the cycloisomerization product **5a** was detected. The formation of **9** follows a carbonyl-ene fragmentation pathway (for a reaction scheme see the Supporting Information).

These are not the final page numbers! **77**

asc.wiley-vch.de

3



Table 3. Cycloisomerization of 1,5-/1,7-enynes.



^[b] Isolated yield.

^[c] 10 mol % Ca(NTf₂)₂ were used.



Scheme 1. Control experiment confirming the proposed reaction pathway.

In summary, a systematic investigation of the π -activation of alkynes with reactive carbocations is presented that explores a reactivity that is complementary to that usually found in transition and noble metalcatalyzed cycloisomerization reactions of enynes. In the presence of 5 mol% of a benign calcium catalyst, ketones of various ring sizes are readily accessed from 1,5-, 1,6- and 1,7-enynes. We are certain that these basic investigations will pave the way for the elaboration of further reactions based on the reaction principles discovered in the area of noble metal catalysis.

Experimental Section

General Procedure

The enyne (0.25 mmol) and MgSO₄·x H₂O (10 mol%) were suspended in 1.5 mL of nitromethane. Bu₄NPF₄ (5 mol%) and Ca(NTf₂)₂ (5 mol%) were added at room temperature and stirred at 50 °C overnight (18 h). For the isolation of the product, 5 mL of saturated NaHCO₃ solution is added, the aqueous phase extracted with dichloromethane, the combined organic phases dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified by column chromatography.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (DFG). Liang Fu receives funding from the China Scholarship Council (CSC).

References

- Selected references: a) A. Fürstner, P. W. Davies, Angew. Chem. 2007, 119, 3478; Angew. Chem. Int. Ed.
 2007, 46, 3410; b) A. S. K. Hashmi, Chem. Rev. 2007, 107, 3180; c) D. J. Gorin, B. D. Sherry, D. F. Toste, Chem. Rev. 2008, 108, 3351; d) E. Jimenez-Nunez, A. M. Echavarren, Chem. Rev. 2008, 108, 3326; e) P. Y. Toullec, V. Michelet, Top. Curr. Chem. 2011, 302, 31.
- [2] a) A. Fürstner, L. Morency, Angew. Chem. 2008, 120, 5108; Angew. Chem. Int. Ed. 2008, 47, 5030; b) A. S. K. Hashmi, Angew. Chem. 2008, 120, 6856; Angew. Chem. Int. Ed. 2008, 47, 6754; c) A. M. Echavarren, Nature Chem. 2009, 1, 431; d) D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. M. Wang, W. A. Goddard, F. D. Toste, Nature Chem. 2009, 1, 482.
- [3] Selected references: a) Y. Yamamoto, I. D. Gridnev, N. T. Patil, T. Jin, *Chem. Commun.* 2009, 45, 5075; b) B. Godoi, R. F. Schumacher, G. Zeni, *Chem. Rev.* 2011, *111*, 2937; c) S. Hummel, S. F. Kirsch, *Beilstein J. Org. Chem.* 2011, 7, 849.
- [4] T. Haven, G. Kubik, S. Haubenreisser, M. Niggemann, Angew. Chem. Int. Ed. 2013, 52, 4016.
- [5] a) W. S. Johnson, L. R. Hughes, J. A. Kloek, T. Niem, A. Shenvi, J. Am. Chem. Soc. 1979, 101, 1281; b) W. S. Johnson, T. M. Yarnell, R. F. Myres, D. R. Morton, S. G. Boots, J. Org. Chem. 1980, 45, 1254; c) A. Furstner, H. Szillat, B. Gabor, R. Mynott, J. Am. Chem. Soc. 1998, 120, 8305; d) A. Balog, S. J. Geib, D. P. Curran, J. Org. Chem. 1995, 60, 345; e) Y. H. Liu, S. L. Zhou, G. J. Li, B. Yan, S. H. Guo, Y. B. Zhou, H. Zhang, P. G. Wang, Adv. Synth. Catal. 2008, 350, 797; f) T. Jin, M. Himuro, Y. Yamamoto, Angew. Chem. 2009, 121, 6007; Angew. Chem. Int. Ed. 2009, 48, 5893; g) T. Jin, J. Uchiyama, M. Himuro, Y. Yamamoto, Tetrahedron Lett. 2011, 52, 2069;

asc.wiley-vch.de

 $\ensuremath{\mathbb S}$ 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

KK These are not the final page numbers!

Adv. Synth. Catal. 0000, 000, 0-0

h) X.-C. Wang, R. L. Yan, M.-J. Zhong, Y.-M. Liang, J. Org. Chem. 2012, 77, 2064.

- [6] Selected references: a) K. K. Yan, B. M. Upton, A. Ellern, A. D. Sadow, J. Am. Chem. Soc. 2009, 131, 15110; b) M. Westerhausen, Z. Anorg. Allg. Chem. 2009, 635, 13; c) P. Jochmann, T. S. Dols, T. P. Spaniol, L. Perrin, L. Maron, J. Okuda, Angew. Chem. 2009, 121, 5825; Angew. Chem. Int. Ed. 2009, 48, 5715; d) S. Harder, Chem. Rev. 2010, 110, 3852; e) O. Michel, H. Kaneko, H. Tsurugi, K. Yamamoto, K. W. Törnroos, R. Anwander, K. Mashima, Eur. J. Inorg. Chem. 2012, 998.
- [7] Selected references: a) M. R. Crimmin, M. Arrowsmith, A. G. M. Barrett, I. J. Casely, M. S. Hill, P. A. Procopiou, J. Am. Chem. Soc. 2009, 131, 9670; b) S. Kobayashi, Y. Yamashita, Acc. Chem. Res. 2011, 44, 58; c) C. Brink-

mann, A. G. M. Barrett, M. S. Hill, P. A. Procopiou, J. Am. Chem. Soc. 2012, 134, 2193; d) T. D. Nixon, B. D. Ward, Chem. Commun. 2012, 48, 11790; e) B. Liu, T. Roisnel, J.-F. Carpentier, Y. Sarazin, Chem. Eur. J. 2013, 19, 2784.

- [8] Selected references: a) M. Niggemann, M. J. Meel, Angew. Chem. 2010, 122, 3767; Angew. Chem. Int. Ed. 2010, 49, 3684; b) M. Niggemann, N. Bisek, Chem. Eur. J. 2010, 16, 11246; c) S. Haubenreisser, M. Niggemann, Adv. Synth. Catal. 2011, 353, 469; d) A. Kena Diba, J.-M. Begouin, M. Niggemann, Tetrahedron Lett. 2012, 53, 6629.
- [9] T. T. Dang, F. Boeck, L. Hintermann, J. Org. Chem. 2011, 76, 9353.

5