ORGANIC LETTERS

2010
Vol. 12, No. 11
2582−2585

Combined $InCl_3$- and Amine-Catalyzed Intramolecular Addition of α-Disubstituted Aldehydes onto Unactivated Alkynes

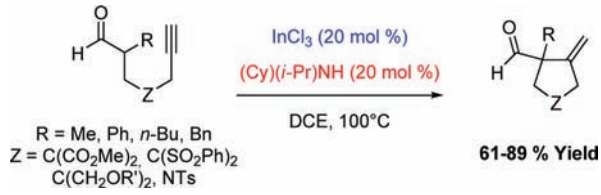
Benjamin Montaignac, Maxime R. Vitale, Veronique Michelet,* and Virginie Ratovelomanana-Vidal*

ENSCP, Chimie ParisTech, UMR 7223, Laboratoire Charles Friedel, 11 rue P. et M. Curie, 75231 Paris Cedex 05, France

veronique-michelet@chimie-paristech.fr; virginie-vidal@chimie-paristech.fr

Received April 6, 2010

ABSTRACT



The combination of enamine-type catalysis to the indium-catalyzed activation of alkynes allows the efficient preparation of functionalized cyclopentanes bearing a quaternary stereogenic center. A broad range of formylalkynyl derivatives has been prepared. The $InCl_3$/(Cy)(*i*-Pr)NH system efficiently promotes the carbocyclization reaction of α-disubstituted aldehydes in good to excellent yields.

Over the past 30 years, transition-metal catalysis[1] and then organocatalysis[2] have known tremendous growth. Despite the broad range of reactions that have been rendered possible through the use of one of these two types of catalysis, there still remain substrates that are unreactive or too sluggish in reactivity. In this context, the concept of combining metal catalysis to organocatalysis has recently flourished and has led to the discovery of several new reactions that would not have been possible without this unusual association.[3] More specifically, it was recently described that the combination of a catalytic quantity of secondary amine and of a catalytic amount of a metal complex (either gold, copper, or palladium) allowed the carbocyclization of keto- or formylalkynes to cyclopentenes.[4] Such a process relies on the formation of a key enamine intermediate, in which the alkyne moiety is activated by the metal complex. Although the carbocyclization reaction goes through the formation of cyclopentanes, in almost all of the cases described in the literature, the presence of an acidic proton (R = H) triggers a rearrangement to the more stable conjugated cyclopentenes with the inconvenient loss of the stereogenic center formerly generated (Scheme 1).

Kirsch et al. have reported that the combination of gold(I)-based catalyst and amine promoted the cyclization

(1) (a) Cornils, B.; Hermann, W. A. *Applied Homogeneous Catalysis with Organometallic Compounds*; Wiley-VCH: New York, 1996. (b) Beller, M.; Bolm, C. *Transition Metals in Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2004. (c) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999. (d) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley-VCH: New York, 2000.

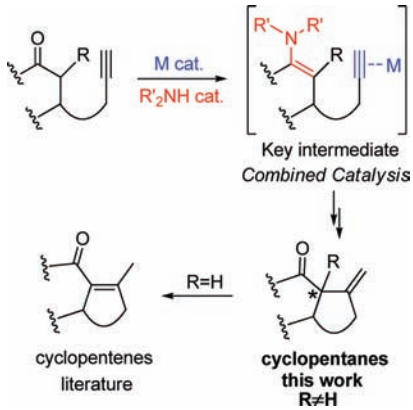
(2) (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) List, B. *Synlett* **2001**, 1675. (c) List, B. *Tetrahedron* **2002**, *58*, 2481. (d) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (e) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005. (f) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (g) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79. (h) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. (i) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, 2007.

(3) (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745, and references cited therein. (b) Zhou, J *Chem.—Asian J.* **2010**, *5*, 422.

(4) (a) Binder, J. T.; Crone, B.; Haug, T. T.; Menz, H.; Kirsch, S. F. *Org. Lett.* **2008**, *10*, 1025. (b) Yand, T.; Ferrali, A.; Campbell, L.; Dixon, D. J. *Chem. Commun.* **2008**, 2923. (c) Zhao, G.-L.; Ullah, F.; Deiana, L.; Lin, L.; Zhang, Q.; Sun, J.; Ibrahem, I.; Dziedzic, P.; Córdova, A. *Chem.—Eur. J.* **2009**, *16*, 1585. (d) Jensen, K. L.; Franke, P. T.; Arróniz, C.; Kobbelgaard, S.; Jørgensen, K. A. *Chem.—Eur. J.* **2010**, *16*, 1750. (e) Yu, C.; Zhang, Y.; Zhang, S.; He, J.; Wang, W. *Tetrahedron Lett.* **2010**, *51*, 1742.

10.1021/ol100729t
Published on Web 05/12/2010

Scheme 1. α-Addition of Aldehydes onto Unactivated Alkynes through Combined Catalysis

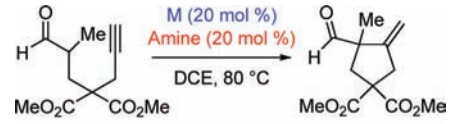


of formyl alkyne derivatives to the corresponding cyclopentenes (R = H) and cyclopentanes (R = Me) in 33−72% yield.[4a] The scope described for this catalytic system in the case of α-methyl-substituted aldehydes was very limited, which prompted us to investigate further this kind of carbocyclization reaction. We report herein a new multicatalytic system, composed of an indium salt and an amine, which allows the general and efficient carbocyclization of a broad range of α-disubstituted formyl alkynes to the corresponding functionalized cyclopentanes bearing a quaternary stereogenic center.

At the outset of our study, the model substrate **1a** was submitted to catalytic amounts (20 mol %) of different metal salts in the presence of a catalytic amount of (*i*-Pr)$_2$NH (20 mol %) in 1,2-dichloroethane at 80 °C (Table 1). Among the different metal catalysts tested, $RuCl_3$, $FeCl_3$, $NiCl_2$, and $RhCl_3$ proved to be rather ineffective in promoting the desired carbocyclization reaction (entries 1−4). The use of $IrCl_3$ or $AgNTf_2$ allowed the reaction to take place, but the conversions of **1a** to **2a** were too slow to constitute good catalytic systems (entries 5 and 6). We next tested the use of indium salts, which have been described by Nakamura et al. to be quite effective catalysts for the addition of *β*-keto ester to unactivated alkynes.[5] $In(OTf)_3$ and $In(NTf_2)_3$ poorly catalyzed the cyclization (entries 7 and 8), whereas $InCl_3$ allowed the complete conversion of the starting material and afforded the desired cyclopentane **2a** in 73% isolated yield (entry 9).

The influence of the amine catalyst was then evaluated. The reactions in the presence of pyrrolidine or (Cy)$_2$NMe were much slower and led, respectively, to 50% and 33%[6] conversion (entries 12 and 13). The use of (Cy)(*i*-Pr)NH allowed a cleaner reaction to take place (entry 14). This last catalytic system was further improved by performing the reaction at 100 °C together with an increase of the substrate concentration to 1 M (entry 15). Given these reaction conditions, the cyclopentane **2a** was obtained in good yield (82%) within 3 h. Two control experiments were done by suppressing each one of the catalysts. The absence of indium trichloride led to the recovery of the starting material (entry 11), and the absence of the amine promoted a complete degradation of **1a** (entry 10). These experiments confirmed the necessity of both catalysts to be present for the carbocyclization to take place.

Table 1. Optimization of Reaction Conditions



1a **2a**

entry	[M]	amine	time (h)	**1a**/**2a**,[a] yield[b] (%)
1	$RuCl_3$	(*i*-Pr)$_2$NH	16	80/20
2	$FeCl_3$	(*i*-Pr)$_2$NH	24	90/10
3	$NiCl_2$	(*i*-Pr)$_2$NH	16	100/0
4	$RhCl_3$	(*i*-Pr)$_2$NH	16	degradation
5	$IrCl_3$	(*i*-Pr)$_2$NH	24	50/50
6	$AgNTf_2$	(*i*-Pr)$_2$NH	24	60/40
7	$In(OTf)_3$	(*i*-Pr)$_2$NH	24	95/5
8	$In(NTf_2)_3$	(*i*-Pr)$_2$NH	20	90/10
9	$InCl_3$	(*i*-Pr)$_2$NH	15	0/100, 73
10	$InCl_3$		5	degradation
11		(*i*-Pr)$_2$NH	15	>99/1
12	$InCl_3$	pyrrolidine	14	50/50
13	$InCl_3$	(Cy)$_2$NMe	14	67/33
14	$InCl_3$	(Cy)(*i*-Pr)NH	14	0/100, 82
15[c]	$InCl_3$	(Cy)(*i*-Pr)NH	3	0/100, 82

[a] Determined by GC of the crude reaction mixture. [b] Isolated yields after column chromatography. [c] Reaction performed at 100 °C, 1 M in substrate.

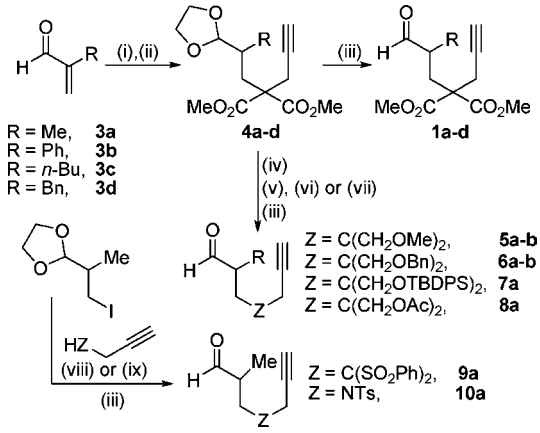
To investigate the scope and limitations of this new catalytic system, a broader range of formyl alkynes has been prepared (Scheme 2). Various α-methylene aldehydes (R = Me, Ph, *n*-Bu, Bn) **3a**−**d** were converted to their corresponding iodo ketals, which upon condensation with dimethyl propargylmalonate afforded the alkynyl derivatives **4a**−**d**. Hydrolysis of these ketals gave access to aldehyde substrates **1a**−**d**, whereas the reduction of their methyl ester groups led to the corresponding diols.

Functionalization of the alcohol moieties followed by deprotection of aldehyde afforded dimethyl ethers **5a**,**b**, dibenzyl ethers **6a**,**b**, disilyl ether **7a**, and diacetate **8a**. Alternatively, the link between the formyl and the alkyne groups was replaced by a *gem*-diphenylsulfone **9a** or

(5) (a) Tsuji, H.; Tanaka, I.; Endo, K.; Yamagata, K.; Nakamura, M.; Nakamura, E. *Org. Lett.* **2009**, *11*, 1845. (b) Itoh, Y.; Tsuji, H.; Yamagata, K.; Endo, K.; Tanaka, I.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 17161. (c) Fujimoto, T.; Endo, K.; Tsuji, H.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 4492. (d) Tsuji, H.; Yamagata, K.; Itoh, Y.; Endo, K.; Nakamura, M.; Nakamura, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 8060. (e) Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 5264. (f) Nakamura, M.; Endo, K.; Nakamura, K. *J. Am. Chem. Soc.* **2003**, *125*, 13002.

(6) It is noteworthy that several unidentified byproducts were also detected by gas chromatography.

Scheme 2. General Synthesis of Substrates **1a**−**d** and **5**−**10** [a]

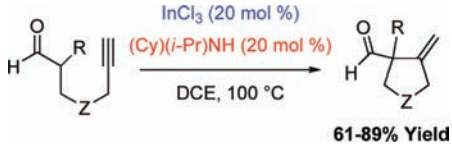


[a] Key: (i) TMSCl, NaI, ethylene glycol, MeCN; (ii) dimethyl propargylmalonate, NaH, DMF; (iii) HCl_{aq}, acetone, H_2O or dioxane/HCOOH/H_2O; (iv) $LiAlH_4$, THF; (v) NaH, MeI, or BnBr/*n*-Bu_4NI (cat.), THF/DMF; (vi) TBDPSCl, imidazole, CH_2Cl_2; (vii) Ac_2O, $(i\text{-Pr})_2NEt$, CH_2Cl_2; (viii) NaH, DMF; (ix) K_2CO_3, DMF.

N-tosyl **10a** groups via alkylation of the corresponding propargyl compounds with the iodide obtained from **3a** followed by the hydrolysis of the ketal moieties.

Under the optimized reaction conditions, the dimethyl ether **5a** and dibenzyl ether **6a** afforded in good yields the corresponding carbocyclization products **11a** (89%) and **12a** (87%) (Table 2, entries 1 and 2). The efficient cyclizations of disilyl ether **7a** and diacetate **8a** further demonstrated the good functional group tolerance of this catalytic system (entries 3 and 4).

Table 2. Carbocyclization of Substrates **1b**−**d** and **5**−**10**



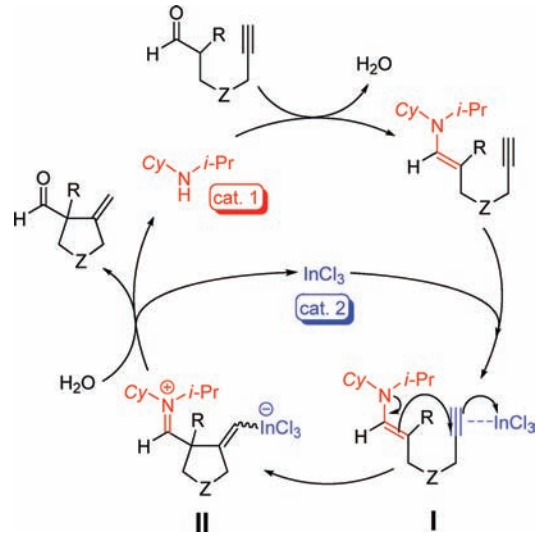
entry	substrate	R	Z	time (h)	product, yield[a] (%)
1	**5a**	Me	$C(CH_2OMe)_2$	13	**11a**, 89
2	**6a**	Me	$C(CH_2OBn)_2$	13	**12a**, 87
3	**7a**	Me	$C(CH_2OTBDPS)_2$	22	**13a**, 88
4	**8a**	Me	$C(CH_2OAc)_2$	18	**14a**, 74
5	**9a**	Me	$C(SO_2Ph)_2$	43	**15a**, 75
6	**10a**[b]	Me	NTs	62	**16a**, 66
7	**1b**	Ph	$C(CO_2Me)_2$	5	**2b**, 61
8	**5b**	Ph	$C(CH_2OMe)_2$	15	**11b**, 86
9	**6b**	Ph	$C(CH_2OBn)_2$	15	**12b**, 79
10	**1c**	*n*-Bu	$C(CO_2Me)_2$	24	**2c**, −
11	**1d**	Bn	$C(CO_2Me)_2$	24	**2d**, −
12[c]	**1c**	*n*-Bu	$C(CO_2Me)_2$	15	**2c**, 71
13[c]	**1d**	Bn	$C(CO_2Me)_2$	15	**2d**, 77

[a] Isolated yields after column chromatography. [b] Reaction performed at 80 °C. [c] $CyNH_2$ was used instead of (Cy)(*i*-Pr)NH.

The more sterically hindered *gem*-diphenylsulfone **9a** also led to cyclopentane **15a** in good yield, despite a longer reaction time (entry 5). Notably, this reaction was extended to the synthesis of pyrrolidine **16a** starting from the *N*-tosyl precursor **10a** (entry 6). This carbocyclization reaction was not limited to substrates bearing a methyl group in the α position relative to the aldehyde moiety (R = Me). Indeed, phenyl-substituted precursors **1b**, **5b**, and **6b** were efficiently cyclized under the optimized reaction conditions (entries 7−9). Unexpectedly, *n*-Bu- and Bn-substituted substrates **1c** and **1d** were very sluggish to react under the optimized reaction conditions and led to degradation products (entries 10 and 11). However, reinvestigation of the catalytic system for these two substrates revealed that the catalytic use of the less sterically demanding primary amine $CyNH_2$ allowed a clean carbocyclization leading to aldehydes **2c** and **2d** in 71% and 77% isolated yield (entries 12 and 13).

Mechanistically, it is reasonable to consider that the condensation of the amine organocatalyst on the aldehyde moiety of the substrate allows the formation of a transient enamine, whereas $InCl_3$ is accountable for the η^2 activation of the alkyne group.[7] The corresponding intermediate **I**, upon nucleophilic addition of the enamine on the alkyne moiety, may evolve toward the iminium vinylindate **II**[8] which, after hydrolysis and protodemetalation, produces the carbocyclization product as well as allows the regeneration of both the amine and indium catalysts (Scheme 3).

Scheme 3. Proposed Mechanism



In summary, we have developed a new catalytic system based on (Cy)(*i*-Pr)NH and $InCl_3$ for the efficient car-

(7) The formation of an indium enolate intermediate as proposed by Nakamura et al. in the case of alkynyl β-keto esters cannot be totally ruled out as the use of the tertiary amine base $(Cy)_2NMe$ led to some reactivity (Table 1).

(8) The steroselectivity of the addition of the enamine toward the alkyne moiety may be *syn* or *anti* and is currently under investigation.

bocyclization of α-disubstituted aldehydes onto unactivated alkynes. We demonstrated that this combination allows the clean cyclization of a broad range of substrates with high yields and a remarkable functional group tolerance. The investigation of an enantioselective version of this reaction is currently underway and will be reported in due course.

Acknowledgment. This work was supported by the Centre National de la Recherche Scientifique (CNRS) and the Ministère de l'Education et de la Recherche for financial support. B.M. is grateful to the Ministère de l'Education et de la Recherche for a grant (2009−2012).

Supporting Information Available: Experimental procedures, characterization of new compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100729T