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$InCl_3/CyNH_2$ Cocatalyzed Carbocyclization Reaction: An Entry to α-Disubstituted *exo*-Methylene Cyclopentanes

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

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

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

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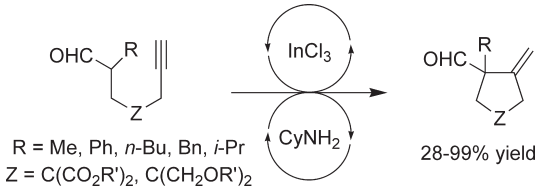
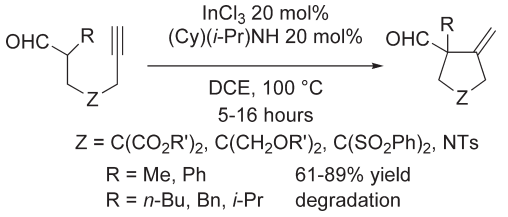


An efficient and cheap synthetic approach to functionalized *exo*-methylene cyclopentanes has been developed from α-disubstituted formyl-alkynes by merging amine catalysis with the indium activation of alkynes. We uncovered the crucial role of the amine cocatalyst and the development of a new cooperative catalytic system allowed the cyclization of a broad range of substrates. A mechanistic study was realized in order to rationalize the determining influence of the amine cocatalyst.

The twentieth century has been the arena of catalysis and has witnessed the emergence of transition metal catalysis[1] and organocatalysis.[2] In 2003, Krische et al. reported that a phosphine organocatalyst in association to a catalytic amount of a palladium (0) complex allowed the cycloallylation of enones.[3] Since this seminal work, the concept of merging organocatalysis to transition metal catalysis has flourished and has opened the way to several new reactivities which would not be possible by either catalysis alone.[4] In this context, enamine organocatalysis was successfully combined to several transition metal activation processes, such as ruthenium, palladium, gold, or copper C−C bond formation.[5] In the context of combining enamine organocatalysis to the metal activation of alkynes, some limitations arise in the case of gold and copper,[5g−k] where either an internal isomerization of the exomethylene function occurred or moderate yields are obtained for disubstituted aldehydes.[5g] We recently investigated the carbocyclization of α-disubstituted formyl-alkynes in the presence of indium (Scheme 1).[6]

SCHEME 1. Combination of Enamine Catalysis to the Metal-Catalyzed Activation of Alkynes



Despite the efficiency of the dual catalytic system composed of a secondary amine, (Cy)(*i*-Pr)NH, and an indium salt, $InCl_3$ for α-methyl and α-phenyl substrates, we encountered a more sluggish reactivity of *n*-butyl, benzyl, or isopropyl corresponding substrates, which led to their degradation in our initially optimized reaction conditions. Considering the high added value of the cyclopentane core,[7] its preparation still requires investigations to allow an efficient and cheap process. We wish to report here an efficient cooperative catalytic system based on the catalytic use of a primary amine and the mechanistic implications during the carbocyclization process.

To find an efficient catalytic system for the carbocyclization of α-disubstituted aldehydes, the model *n*-butyl-substituted alkynyl derivative **1** was initially submitted to 20 mol % of $InCl_3$ salts in the presence of 20 mol % of various amines in 1,2-dichloroethane at 100 °C (Table 1). The use of (Cy)-(*i*-Pr)NH led mainly to the formation of degradation products after prolonged reaction times (Table 1, entry 1). We anticipated that this lack of reactivity could arise from the

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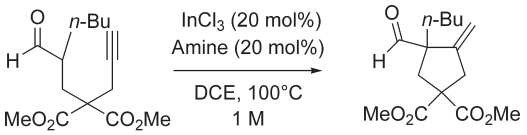
TABLE 1. Optimization of the Amine Catalyst for Hindered Substrates



1 **2**

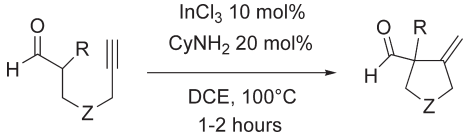
entry	amine	t (h)[a]	yield (%)[b]
1 [ref6]	Cy(*i*-Pr)NH	72	
2	Bn_2NH	62	36
3	BnMeNH	80	36
4	$(n\text{-Pr})_2NH$	62	25
5	Et_2NH	62	nd
6	n-$BuNH_2$	40	nd
7	$BnNH_2$	48	34
8	$CyNH_2$	0.7	81
9	i-$PrNH_2$	6	73
10	(±)-$PhMeCHNH_2$	2.5	74
11	t-$BuNH_2$	40	nd
12	$C_6H_5NH_2$	24	47
13	p-$MeOC_6H_4NH_2$	100	48
14	p-$NO_2C_6H_4NH_2$	6	22
15	$CyNH_2$	1	80[c]
16	$CyNH_2$	7	80[d]

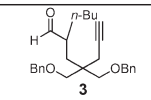
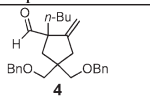
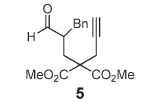
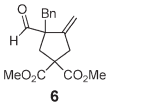
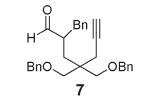
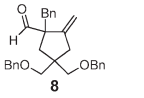
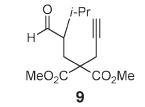
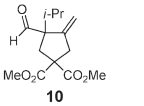
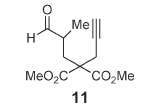
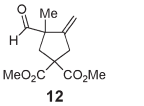
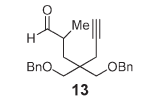
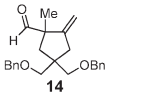
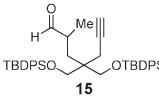
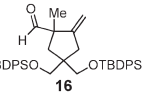
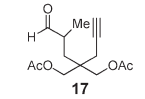
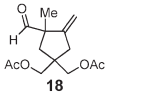
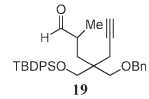
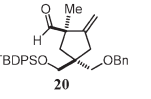
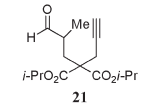
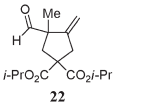
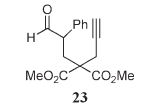
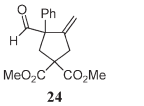
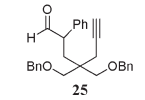
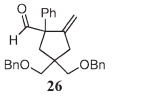
[a]Time to reach full GC conversion of **2**. [b]Isolated yield. [c]10 mol % of $InCl_3$. [d]5 mol % of $InCl_3$.

enhanced allylic strains generated by bulky groups in α-position of the aldehyde moiety and the rather encumbered secondary amine (Cy)(*i*-Pr)NH during the enamine formation. Less bulky secondary amines such as Bn_2NH, BnMeNH, $(n\text{-Pr})_2NH$, or Et_2NH were therefore tested. Although those amines allowed the desired cyclopentane **2** to be formed to some extent, the reactivity was still sluggish and the formation of several unidentified byproducts was observed. As a result, only moderate yields (25−36%) could be obtained while using secondary amines (Table 1, entries 2−5).

The use of linear primary amines such as *n*-butylamine or *N*-benzylamine resulted in slow cyclization reactions in competition with degradation processes (Table 1, entries 6 and 7). A striking difference was observed when more hindered and more electron-rich α-disubstituted primary amines were used. Indeed, $CyNH_2$, i-$PrNH_2$, or racemic $PhMeCHNH_2$ allowed the carbocyclization reaction, very rapidly and cleanly, and led to the desired cyclopentane **2** in 73−81% isolated yields (Table 1, entries 8−10). On the other hand, the use of α-trisubstituted primary amine t-$BuNH_2$ only led to degradation (Table 1, entry 11). Anilines with different electronic properties were also evaluated. Although aniline and *p*-OMe aniline induced the formation of the desired cyclopentane, the cyclization reactions were slow and led only to moderate isolated yields (47−48%) (Table 1, entries 12 and 13). A faster reaction took place with the electron-poor p-NO_2 aniline; however, **2** was obtained in poor yield (Table 1, entry 14). Therefore, $CyNH_2$ was selected as amine catalyst for the cyclization of hindered substrates. Notably, the use of lower indium catalyst loadings was not detrimental to the carbocyclization reaction. Indeed, 10 mol % of $InCl_3$ did not significantly affect the kinetics of the cyclization, nor the yield in cyclopentane **2** (Table 1, entry 15), whereas 5 mol % of $InCl_3$ resulted in a slower, yet clean, reaction (Table 1, entry 16). Consequently, the catalytic system composed of 10 mol % of $InCl_3$ and 20 mol % of $CyNH_2$ was chosen for the cyclizations of a broader range of α-branched formyl alkynes (Table 2).

TABLE 2. Substrate Scope of the $InCl_3/CyNH_2$ Catalytic System

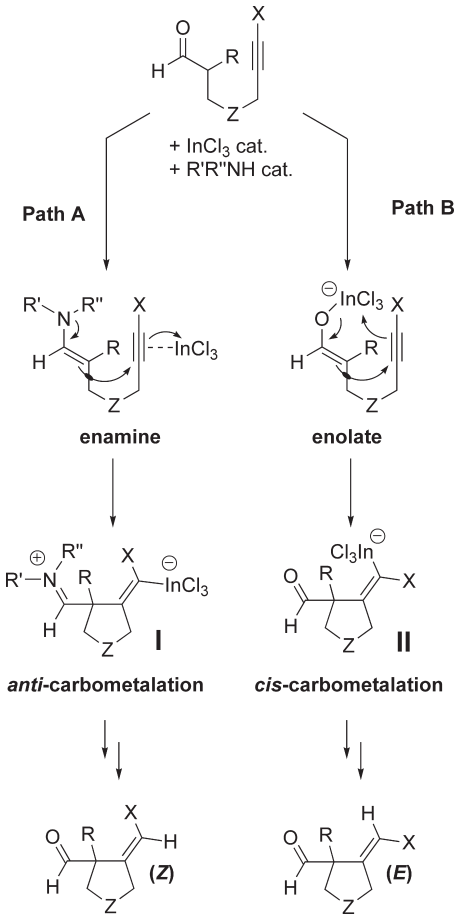


entry	substrate	product	yield (%)[a]
1	 **3**	 **4**	94
2	 **5**	 **6**	80
3	 **7**	 **8**	99
4	 **9**	 **10**	28[b]
5	 **11**	 **12**	83
6	 **13**	 **14**	88
7	 **15**	 **16**	95
8	 **17**	 **18**	81
9	 **19**	 **20**	91[c]
10	 **21**	 **22**	91
11	 **23**	 **24**	85
12	 **25**	 **26**	94

[a]Isolated yield. [b]20 mol % of $InCl_3$, 160 h. ^{1}H NMR of the crude indicates a 20/80 **9**/**10** ratio and the formation of several unidentified byproducts. [c]dr = 1.75/1 determined by ^{1}H NMR of the crude reaction mixture (major diastereomer is shown).

The $InCl_3/CyNH_2$ catalytic system proved to be very efficient for the carbocyclization of other hindered substrates such as *n*-butyl-substituted substrate **3** and benzyl-substituted substrates **5** and **7**. Indeed, cyclopentanes **4**, **6**, and **8** were all obtained in good yields up to 99% (Table 2, entries 1−3).

SCHEME 2. Possible Mechanisms

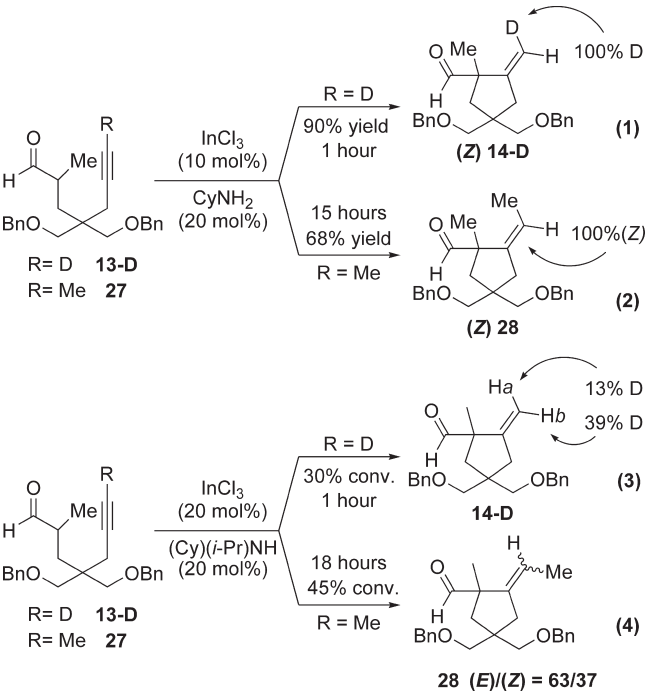


As expected, when the reaction was conducted in the presence of the much hindered precursor **9** (R = *i*-Pr), a significant decrease of reactivity was observed but **10** was isolated in 28% yield (Table 2, entry 4).

This new catalytic system was also evaluated in the carbocyclizations of diversily functionalized methyl-substituted and phenyl-substituted formyl-alkynes, **11**, **13**, **15**, **17**, **21**, **23**, and **25**. It is noteworthy that, in all cases better results were obtained both in terms of reactivity and isolated yield than in the presence of the (Cy)(*i*-Pr)NH/$InCl_3$ catalytic system that we previously described[6] (Table 2, entries 4−8 and 10−12). The reaction of the dissymmetric substrate **19** provided cyclopentanes **2f** in excellent yield and moderate diastereoselectivity (Table 2, entry 9).

The presence of both the $InCl_3$ and amine catalysts was required for the carbocyclizations to take place, thus emphasizing the necessity of combining catalysis for this reaction.[8] Mechanistically, two pathways may be envisioned. The nucleophilic addition of a secondary or primary amine on the aldehyde moiety would lead to the formation of an enamine, whereas $InCl_3$ would be responsible for the activation of the alkyne moiety. Following this hypothesis, the *anti* nucleophilic addition of the enamine on the activated alkyne would lead

SCHEME 3. Carbocyclization of Deuterium-Labeled and Nonteminal Alkyne Substrates 13-D and 27



to the vinyl indium species **I**,[9] which, after protodemetalation and hydrolysis, would afford the carbocyclization product (Scheme 2, path A). The second pathway would imply an indium enolate, resulting from the amine-induced α-deprotonation of the aldehyde moiety. Nakamura et al. recently demonstrated that such indium enolate species are involved in the addition of 1,3-dicarbonyl compounds onto alkynes, and that the carbometalation step then proceeds in a cis manner.[10] According to this second reaction mechanism the vinyl indium **II** would be generated, and would evolve, after protodemetalation, to the corresponding cyclopentane (Scheme 2, path B).

To obtain some insights on the nature of the reaction mechanism(s) involved, the deuterium-labeled substrate **13-D** and the nonterminal alkyne **27** were prepared and engaged with the $InCl_3/CyNH_2$ catalytic systems. The use of the $InCl_3/CyNH_2$ catalytic system afforded exclusively a single isomer of **14-D** with 100% deuterium at the cis position,[11] and no D−H scrambling was detected. In the case of the methyl-substituted alkyne **27**, the $CyNH_2$-based catalytic system led exclusively to the formation of the (*Z*) isomer of **28** (Scheme 3, eq 2).[11] The primary amine $CyNH_2$ would therefore promote the enamine/*anti*-carbometalation reaction mechanism (Scheme 2, path A).

We also compared these results with the previously reported system: when the (Cy)(*i*-Pr)NH/$InCl_3$ catalytic system

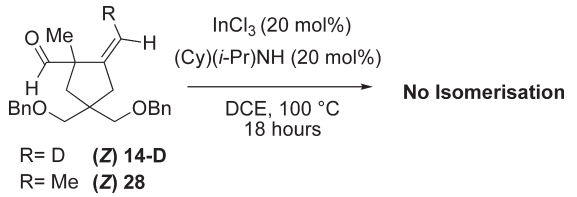
(8) The reaction without $InCl_3$ leads to the recovery of the starting material, whereas the absence of amine promotes the rapid degradation of the cyclization precursor.

(9) For an example of $InCl_3$-catalyzed trans-addition to alkynes, see: Miura, K.; Fujisawa, N.; Toyohara, S.; Hosomi, A. *Synlett* **2006**, 1883.

(10) For an example of $InCl_3$-catalyzed cis-addition to alkynes, see: (a) Tsuji, H.; Tanaka, I.; Endo, K.; Yamagata, K.-I.; Nakamura, M.; Nakamura, E. *Org. Lett.* **2009**, *11*, 1845. (b) Itoh, Y.; Tsuji, H.; Yamagata, K.-I.; 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, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002.

(11) Alkene geometry was determined by NOESY NMR experiments. Please see the Supporting Information for more details.

SCHEME 4



was used, a mixture of deuterated and nondeuterated adducts was obtained. The cyclization product **14-D** was formed with 13% deuterium at the cis position (H*a*) and 39% deuterium at the trans position (H*b*) (Scheme 3, eq 3).

A considerable amount of D−H exchange occurred during the reaction, which led to the formation of 30% diprotonated **14-H$_2$** together with the formation of 18% dideuterated **14-D$_2$**[12] (Scheme 3, eq 3).

The secondary amine based catalytic system consistently led to the formation of a (*E*)/(*Z*) mixture of cyclopentane **28** (Scheme 3, eq 4), where the (*E*) isomer was formed preferentially.

Considering that the high Lewis acidity of $InCl_3$ could be responsible of a thermodynamically favored isomerization of the double bond postcyclization, we engaged (*Z*)-**14-D** and (*Z*)-**28** with the secondary amine based catalytic system (Scheme 4). However, no isomerization was observed in those reaction conditions after 18 h. Therefore, in contrast with the previous case, the secondary amine (Cy)(*i*-Pr)NH would favor the enolate/cis-carbometalation pathway (Scheme 2, path B) in competition with the enamine/*anti*-carbometalation process.

In summary, we have developed an efficient and cheap system based on the combination of $InCl_3$ and a primary amine $CyNH_2$ that allowed the carbocyclization of α-disubstituted aldehydes onto unactivated alkynes to form readily functionalized cyclopentanes. This study showed that the primary amine-based catalytic system has a broad scope as it could be used for the cyclization of hindered α-disubstituted aldehydes. From the mechanistic point of view, we demonstrated that the amine cocatalyst has a direct influence on reaction pathway. It favors either the formation of an indium enolate reactive species that undergoes a cis-carbometalation, or the formation of an enamine that evolves through *anti*-carbometalation.

(12) An acetylenic D−H exchange (64% D−36% H) was observed when submitting **13-D** to 20 mol % (Cy)(*i*-Pr)NH at 100 °C in DCE during 2 h without $InCl_3$. Thus, the scrambling may result from an acid−base equilibrium.

Experimental Section

General Procedure for the Carbocyclization Reactions. In a sealed vial were successively introduced freshly purified formyl alkyne (0.4 mmol, 1 equiv), a freshly prepared 0.2 M solution of amine in DCE (400 μL, 0.08 mmol, 0.2 equiv), and $InCl_3$ (0.08 mmol, 0.2 equiv). The reaction mixture was stirred at 100 °C until GC or TLC analysis indicated complete conversion, and then 1 mL of an aqueous solution of AcOH (1/1 v/v) was added at room temperature. The resulting mixture was stirred 15 min at room temperature and then was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by silica gel flash chromatography to afford the desired cyclopentane.

4,4-Bis(benzyloxymethyl)-1-butyl-2-methylene-cyclopentanecarbaldehyde (4): 94% yield; colorless oil; ^{1}H NMR (300 MHz, C_6D_6) δ 9.21 (s, 1H), 7.35−7.03 (m, 10H), 4.98 (t, J = 1.8 Hz, 1H), 4.76 (t, J = 2.0 Hz, 1H), 4.45−4.18 (m, 4H), 3.34 (s, 4H), 2.54 (d, J = 14.0 Hz, 1H), 2.38 (dt, J = 15.9, 1.8 Hz, 1H), 2.24 (d, J = 15.0 Hz, 1H), 1.69−1.52 (m, 1H), 1.60 (d, J = 15,0 Hz, 1H), 1.42−1.27 (m, 1H), 1.21−0.93 (m, 4H), 0.77 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 200.1, 152.2, 139.3, 139.3, 128.5, 127.7, 109.4, 73.8, 73.6, 73.4, 73.4, 61.1, 46.3, 40.7, 36.4, 35.6, 27.2, 23.5, 14.1; HRMS calcd for $C_{27}H_{34}O_3Na$ 429.24002, found 429.23960.

1-Benzyl-4,4-bis(benzyloxymethyl)-2-methylene-cyclopentanecarbaldehyde (8): 99% yield; colorless oil; ^{1}H NMR (300 MHz, C_6D_6) δ 9.32 (s, 1H), 7.25−6.89 (m, 15H), 4.98 (t, J = 2.0 Hz, 1H), 4.78 (t, J = 2.0 Hz, 1H), 4.21 (s, 4H), 3.23 (s, 2H), 3.17 (s, 2H), 2.97 (d, J = 13.8 Hz, 1H), 2.67 (d, J = 13.8 Hz, 1H), 2.27 (d, J = 14.3 Hz, 1H), 2.21−2.13 (m, 2H), 1.78 (d, J = 14.3 Hz, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 199.6, 152.0, 139.3, 139.2, 137.8, 130.6, 128.5, 128.5, 126.8, 110.3, 73.7, 73.4, 73.3, 73.3, 62.0, 46.6, 42.3, 41.1, 35.4; HRMS calcd for $C_{30}H_{32}O_3Na$ 463.22437, found 463.22372.

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