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PAPER

Copper(I)–amine metallo-organocatalyzed synthesis of carbo- and heterocyclic systems†‡

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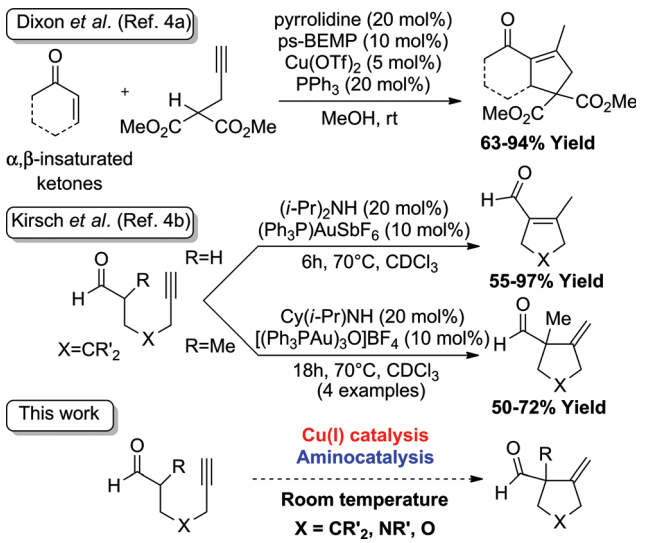
The efficient and atom economical synthesis of 5-membered cyclic structures has been achieved through the combination of amino catalysis and metal catalysis. The discovery of a novel metallo-organocatalytic system merging the use of a catalytic copper(I) complex and a catalytic amount of cyclohexylamine allowed the room temperature preparation of a broad range of skeletons such as cyclopentanes, indanes, pyrrolidines and tetrahydrofuran, important structural cores of many biologically relevant molecules. Mechanistic studies were presented.

Introduction

During recent years, the emergence of a new concept that merges transition metal catalysis[1] to organocatalysis[2] has been highlighted.[3] The success of such original approach relies on the fact that the association of both kinds of activations allowed several new types of reactivities and/or original ways of controlling stereoselectivities to be unveiled.[3] Several groups including us have been interested in this concept in the presence of various transition metals and carbophilic Lewis acids.[3–6] In 2008, Dixon's and Kirsch's groups respectively described the carbocyclization of keto and formyl alkynes through the combination of metal catalysis with aminocatalysis (Scheme 1).[4,5] Whereas both dual catalytic systems were highly efficient for the synthesis of cyclopentene cores, the preparation of analogous cyclopentanes bearing a quaternary stereogenic center was comparatively less studied. For this particular transformation, Kirsch *et al.* described, on a limited substrate scope, a catalytic system based on the use of a secondary amine and a rather high catalyst loading of a gold(I) complex. In 2010, we reported that the carbocyclization of α-disubstituted formyl alkynes could be successfully realized using a catalytic quantity of a secondary or primary amine, and a catalytic amount of cheap indium trichloride.[6,7] These indium/amine based catalytic systems allowed, with good to excellent yields, the preparation of a broad variety of cyclopentanes, an important structural core of many biologically relevant molecules including prostaglandins.[8] As a major drawback of these metallo-organocatalytic systems, the rather harsh reaction conditions generated by elevated temperature (100 °C) and by highly Lewis acidic indium trichloride[9] limited their use to the synthesis of carbon tethered 5-membered cyclic systems. In the search of a milder combination, we recently turned our attention toward the use of copper(I) transition metal complexes. Balme *et al.* previously reported that the copper(I) catalyzed *anti*-carbocupration of stabilized nucleophiles onto non-activated alkynes could be realized at room temperature.[10] On the other hand, Dixon *et al.* used such metal complexes for the preparation of cyclopentenes,[4a] and also reported the use of copper(I) complexes in association with a



Scheme 1 Aim of this work.

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† Dedicated to Dr C. Bruneau on the occasion of his 60th birthday.

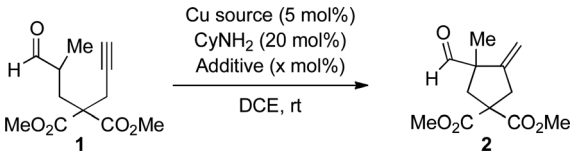
‡ Electronic supplementary information (ESI) available: General cyclization procedure and analytical descriptions of all substrates and carbocyclization products. See DOI: 10.1039/c2ob06449a

cinchona based thiourea organocatalyst for a room temperature and enantioselective version of the Conia-ene reaction of β-keto esters.[11] Following our previous communication concerning an original copper(I) based metallo-organocatalytic system allowing the mild carbocyclization of a broad range of carbon and few nitrogen tethered substrates,[12] we report herein a comprehensive study including the synthesis of cyclopentane, indane, pyrrolidine and tetrahydrofuran skeletons (Scheme 1) and presenting mechanistic insights.

Results and discussion

The optimization of the catalytic system was obtained while investigating the carbocyclization reaction of the model substrate **1**. A recent study in our group demonstrated the strong influence of the amine co-catalyst over the reaction pathway of related metallo-organocatalyzed carbocyclization reactions.[6b] Accordingly, cyclohexylamine was selected as the best organocatalyst partner due to its high aptitude for generating enamine intermediates from α-disubstituted aldehydes. The screening of different copper sources was carried out at room temperature in 1,2-dichloroethane with 5 mol% of metal catalyst loading, 20 mol% of organocatalyst and, in some cases, 5–20 mol% of additive (Table 1). Firstly, copper(I) iodide was evaluated and showed poor reactivity, with or without triphenylphosphane additive and despite long reaction times (Table 1, entries 1–3). This led us to use the presumably more electrophilic tetrakis acetonitrile copper(I) complexes. A slight improvement of the conversion was observed with the tetrafluoroborate salt (Table 1, entries 4–5), which could be further enhanced using an equimolar amount of triphenylphosphane additive, to reach 70% after 64 h (Table 1, entry 6). Following this last result, the addition of 10 mol% triphenylphosphane to this copper complex was tried but led to a significant drop of reactivity (Table 1, entry 7). To evaluate the importance of the counter-anion, the perchlorate and trifluoromethanesulfonate salt of these tetrakis copper(I) complexes were also tested but both gave either similar or shoddier results (Table 1, entries 8–9). The influence of the phosphane additive was then considered, but neither the more electron rich tricyclohexylphosphane, nor the electron poorer tris (*p*-trifluoromethylphenyl)phosphane improved the efficiency of the catalytic system (Table 1, entries 10–11). Finally, the use of copper(I) triflurormethanesulfonate–benzene complex allowed the reaction to be complete in 16 h at room temperature, providing the targeted cyclopentane **2** in an encouraging 65% isolated yield (Table 1, entry 12). However, attempts to improve both the catalytic activity and the yield with this copper source while adding triphenylphosphane additive were unsuccessful (Table 1, entry 13). Considering the well-known instability of copper(I) trifluoromethanesulfonate–arene complexes, we then considered generating the copper(I) catalytic species by the *in situ* reduction of copper(II) salts.[13,4a]

Table 1 Optimization of copper based metallo-organocatalytic systems



Entry	Copper source (5 mol%)	Additive (*x* mol%)	Time (h)	SM/P[a]
1	CuI	—	16	>95/5
2	CuI	—	2 w	50/50
3	CuI	PPh_3 (15)	16	>95/5
4	$[Cu(MeCN)_4]BF_4$	—	16	88/12
5	$[Cu(MeCN)_4]BF_4$	—	64	66/34
6	$[Cu(MeCN)_4]BF_4$	PPh_3 (5)	64	30/70
7	$[Cu(MeCN)_4]BF_4$	PPh_3 (10)	64	85/15
8	$[Cu(MeCN)_4]ClO_4$	PPh_3 (5)	64	30/70
9	$[Cu(MeCN)_4]OTf$	PPh_3 (5)	64	70/30
10	$[Cu(MeCN)_4]BF_4$	PCy_3 (5)	48	50/50
11	$[Cu(MeCN)_4]BF_4$	$P(p\text{-}CF_3C_6H_4)_3$ (5)	48	35/65
12	Cu(OTf)·½benzene	—	16	<5/95[b]
13	Cu(OTf)·½benzene	PPh_3 (15)	16	87/13
14	$Cu(OTf)_2$	PPh_3 (5)	16	76/24
15	$Cu(OTf)_2$	PPh_3 (20)	22	<5/95[c]
16	$CuBr_2$	PPh_3 (20)	16	90/10
17	$Cu(OAc)_2$	PPh_3 (20)	16	85/15
18	$CuSO_4{\cdot}5H_2O$	PPh_3 (20)	16	>95/5

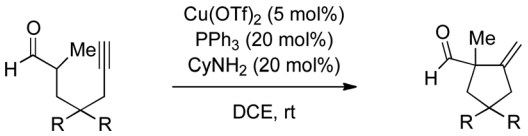
[a] Determined from ^1H NMR of the crude reaction mixture. [b] 65% isolated yield. [c] 86% isolated yield.

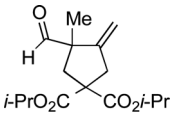
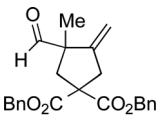
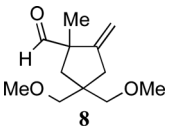
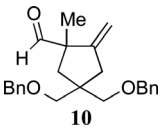
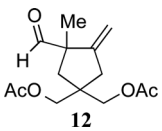
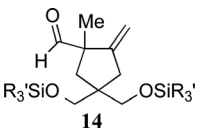
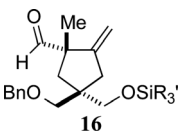
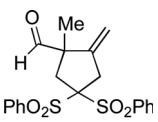
Although the reduction of copper(II) trifluoromethanesulfonate by an equimolar amount of triphenylphosphane led to moderate reactivity (Table 1 entry 14), the use of four equivalents of phosphane allowed full conversion in 22 h yielding **2** in good 86% yield (Table 1, entry 15). Under these reaction conditions, several other copper(II) salts including $CuBr_2$, $Cu(OAc)_2$ and $CuSO_4{\cdot}5H_2O$ were tested but none of them provided a better result than the one obtained with $Cu(OTf)_2$ precatalyst (Table 1, entries 16–18). For the purpose of our study, we thus selected the catalytic system consisting of 5 mol% $Cu(OTf)_2$, 20 mol% triphenylphosphane and 20 mol% of cyclohexylamine.

The scope of this catalytic system was then studied starting with the evaluation of a range of α-methyl carbon tethered formyl-alkynes (Table 2). The use of bulkier diisopropyl- or dibenzylmalonate links did not influence the efficiency of the carbocyclization reaction, as cyclopentanes **4** and **6** were isolated in 82% and 89% yield respectively (Table 2, entries 1–2). Fortunately, this catalytic system displayed a good tolerance to many functional groups such as ether, ester and silylether moieties, leading to the corresponding carbocyclized products **8**, **10**, **12** and **14** in yields above 90% (Table 2, entries 3–6). While reacting the nonsymmetrical tethered substrate **15**, a good global yield was obtained, although a poor diastereoselectivity of this process was observed (Table 2, entry 7). Interestingly, the *gem*-disulfone **17** smoothly cyclized under these conditions whereas this particular substrate led to retro-Michael side process under our previously developed $CyNH_2/InCl_3$ catalytic system (Table 2, entry 8).[6b]

Diversely α-substituted carbon tethered substrates were prepared and submitted to cyclization in order to assess the influence of the α-substitution pattern of the aldehyde moiety. Results are gathered in Table 3. The α-ethyl dimethylmalonate substrate **19** required a longer reaction time to reach full conversion of the starting material and yielded 67% of cyclopentane **20** (Table 3, entry 1). Similarly, the α-n-butyl and α-benzyl analogs reacted slowly, and 90 h were required for completion.

Table 2 Carbocyclization reactions of α-methyl substituted carbon tethered substrates

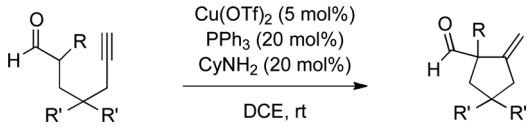


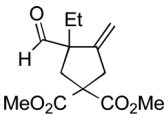
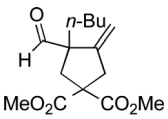
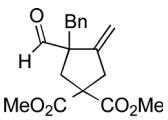
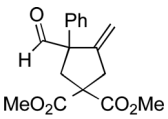
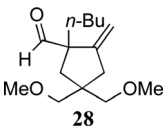
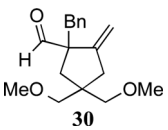
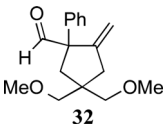
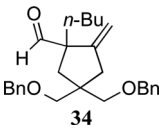
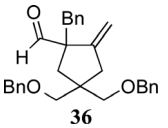
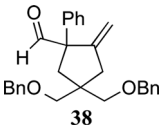
Entry	Substrate R	Product	*t* (h)	Yield[a] (%)
1	**3** CO_2i-Pr	 **4**	16	82
2	**5** CO_2Bn	 **6**	17	89
3	**7** CH_2OMe	 **8**	16	92
4	**9** CH_2OBn	 **10**	16	95
5	**11** CH_2OAc	 **12**	19	93
6	**13** $CH_2OSiR'_3$[b]	 **14**	22	94
7	**15** CH_2OBn/ $CH_2OSiR'_3$[b]	 **16**	17	93[c]
8	**17** SO_2Ph	 **18**	17	92

[a] Isolated yield. [b] $OSiR'_3$ = $OSi(t\text{-Bu})(Ph)_2$. [c] dr = 60/40, major diastereoisomer is shown (determined by NOESY NMR experiment).

Corresponding cyclopentanes **22** and **24** were obtained in moderate 62% and 68% yields respectively, due to the appearance of some unidentified by-products after extended reaction times (Table 3, entries 2–3). This trend was confirmed with the α-phenyl substituted substrate **25** for which the cyclization was inefficient at room temperature and needed to be run at 50 °C in order to observe reasonable reactivity. Under these modified reaction conditions, cyclopentane **26** was obtained in 90% isolated yield (Table 3, entry 4). Notably, the cyclizations of the

Table 3 Carbocyclization reactions of diversely α-substituted carbon tethered substrates



Entry	Substrate R/R′	Product	*t* (h)	Yield[a] (%)
1	**19** Et/CO_2Me	 **20**	64	67
2	**21** *n*-Bu/CO_2Me	 **22**	64 90	48[b] 62
3	**23** Bn/CO_2Me	 **24**	90	68
4	**25** Ph/CO_2Me	 **26**	28	90[c]
5	**27** *n*-Bu/CH_2OMe	 **28**	136	—[d]
6	**29** Bn/CH_2OMe	 **30**	72	87
7	**31** Ph/CH_2OMe	 **32**	24	90
8	**33** *n*-Bu/CH_2OBn	 **34**	90	92
9	**35** Bn/CH_2OBn	 **36**	72	87
10	**37** Ph/CH_2OBn	 **38**	54	92

[a] Isolated yield. [b] Incomplete conversion was observed: **21**/**22** = 20/80. [c] Reaction performed at 50 °C. [d] **27**/**28** = 30/70

n-butyl and the benzyl substrates **21** and **23** were not significantly improved working at 50 °C. Therefore, the bulkiness of

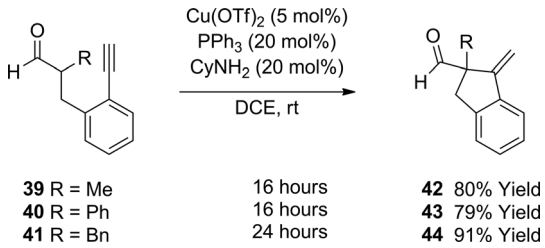
the R group in the α position of the aldehyde moiety seems to have a key influence on the efficiency of cyclization, larger groups inducing a substantial decrease in reactivity. Analogous substrates in which the methylester moieties were replaced either by methoxymethyl or benzyloxymethyl groups were also engaged in the process. Aside from the peculiar sluggish reactivity of the n-butyl *gem*-dimethoxymethyl substrate **27** (Table 3, entry 5), most of these precursors gave better results than their malonate counterparts, both in term of isolated yields and reaction times. Accordingly, *gem*-dimethoxymethyl cyclopentanes **30** and **32** were obtained in good yields, 87% and 90% respectively (Table 3, entries 6–7), and their *gem*-dibenzyloxymethyl equivalents **34**, **36** and **38** were generated in an average yield of 90% (Table 3, entries 8–10).

Subsequently, we focused on the metallo-organocatalytic cyclization of aromatic tethered substrates as it would allow the preparation of indanes, important constituents of biologically active natural products and compounds exhibiting pharmacological properties (Scheme 2).[14]

Gratifyingly, the dual catalytic system described herein allowed the clean carbocyclization of the synthesized formyl alkynes **39**, **40**, and **41** and led to the corresponding indanyl derivatives **42**, **43** and **44** in good to excellent yields (Scheme 2, 79–91%). In contrast with the previously studied carbon tethered formyl alkynes (Tables 2 and 3), scarce influence of the R group in regard to the efficiency or rate of the cyclization reactions was observed while using these aromatic tethered substrates.

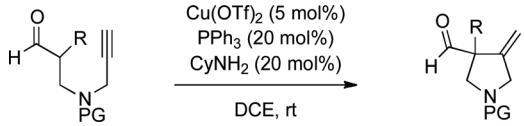
We then envisioned the use of this copper(I) based metallo-organocatalytic system for the preparation of pyrrolidines, likewise key skeletons in many biologically active natural and non-natural substance.[15] Therefore, several nitrogen tethered substrates were prepared and submitted to cyclization (Table 4).

Starting from the *N*-tosyl α-methyl substituted substrate **45**, a very smooth reaction led in only two hours to the desired *N*-tosyl pyrrolidine **46** in 86% yield (Table 4, entry 1). This reaction could also be efficiently realized starting from the *N*-benzoyl protected analogous substrate **47** (79%, Table 4, entry 2). Similarly, the α-n-butyl and the functionalized α-benzyloxyethyl *N*-tosyl pyrrolidines **50** and **52** were obtained in good yields in few hours (Table 4, entries 3–4). The α-benzyl and α-phenyl substrate **53** and **55** afforded their corresponding heterocyclized derivatives with excellent yields despite longer reaction times (23–24 h, Table 4, entries 5–6). In the case of **53**, difficulties in monitoring the cyclization led us to arbitrarily conduct the reaction in 24 h in order to ensure full conversion of the starting material. However, in the case of the phenyl substituted substrate **55**, the intermediate formation of 2-phenylpropenal was observed by ^{1}H NMR spectroscopy,[16] which clearly indicated



Scheme 2 Metallo-organocatalytic preparation of indanes.

Table 4 Metallo-organocatalytic preparation of pyrrolidines

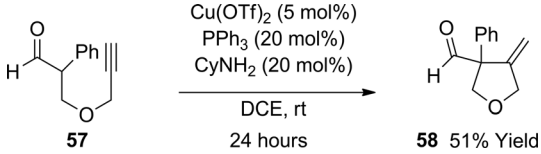


Entry	Substrate R/PG	Product	*t* (h)	Yield[a] (%)
1	**45** Me/Ts	**46**	2	86
2	**47** Me/COPh	**48**	4	79
3	**49** *n*-Bu/Ts	**50**	6	91
4	**51** $(CH_2)_2$OBn/NTs	**52**	4	89
5	**53** Bn/NTs	**54**	23	96
6	**55** Ph/NTs	**56**	24	91

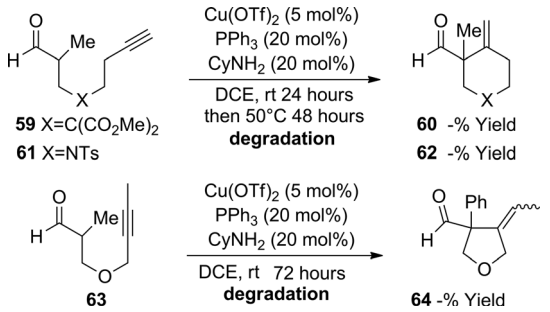
[a] Isolated yield.

that, in this particular case, a parallel reversible retro-Michael process also took place. This side-reaction could explain why the overall cyclization rate of the phenyl substituted substrate **55** decreased, and why 24 h were required for completion. Notably, we encountered a comparable retro-Michael side process in the case of the oxygen tethered substrate **57**. Its cyclization led to the corresponding derivative **58** in 51% yield, thus expanding our metallo-organocatalytic approach to the synthesis of tetrahydrofuran cores (Scheme 3).

In order to evaluate the efficiency of this metallo-organocatalytic system for the formation of larger rings such as



Scheme 3 Metallo-organocatalytic preparation of tetrahydrofuran **58**.



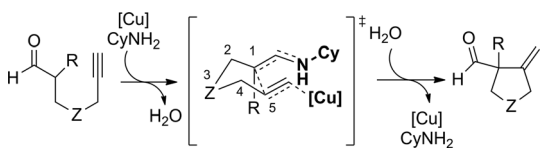
Scheme 4 Cyclization of homo-propargyl compounds and a non-terminal alkyne.

cyclohexanes or piperidines, substrates **59** and **61** were prepared and submitted to cyclization (Scheme 4). In both cases, the catalytic system described herein did not promote the desired cyclization at room temperature whereas prolonged heating of the reaction mixture at 50 °C led to complete degradation of starting materials. Therefore, this method, although fairly efficient for the synthesis of 5-membered carbo- and heterocycles, seemed inadequate for the formation of analogous 6-membered rings. Additionally, the cyclization of the non-terminal alkyne **63** gave rise, at room temperature, to its slow degradation which was consistent with the previously reported sluggish copper(I)-mediated 5-*exo*-dig cyclization of malonates onto disubstituted alkynes,[10b] and underlined the poor stability of such precursors. Consequently, this methodology could not be extended to the use of formyl alkynes possessing a disubstituted alkynyl moiety.

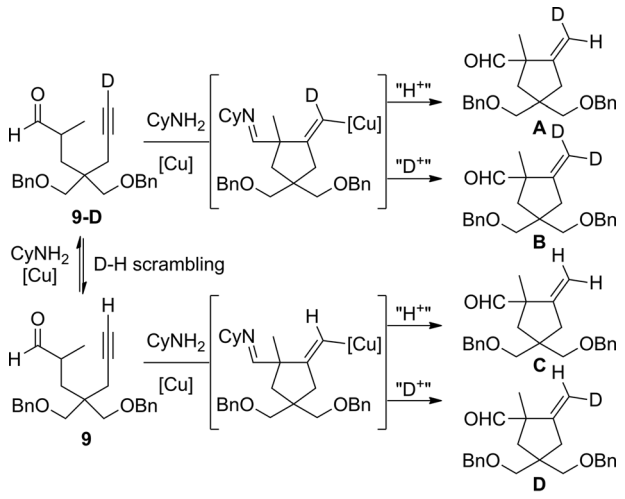
The reaction rate discrepancies observed during the investigation of this broad range of carbon, aromatic, nitrogen and oxygen tethered substrates prompted us to look at mechanistic implications. We suggest that the rate determining step of this reaction, apart from the cases in which retro-Michael took place, would be the attack of the transient enamine onto the copper(I) activated alkyne moiety,[17] and moreover, that it would occur according to a chair like transition state (Scheme 5).

This mechanistic picture is supported by the fact that hindered carbon tethered substrates, in which R is different from a methyl group, were more sluggish to react (Table 2). On one hand, the development of deleterious 1,3-diaxial strains would disfavor the required transition state conformation and therefore slow down the cyclization process. On the other hand, aromatic and nitrogen tethered precursors were poorly dependant on the steric hindrance generated by the group in α-position of the aldehyde moiety. With respect to these precursors, we could assume that the sp^2 geometry[18] at the 3 position would set the transition state free from these detrimental 1,3-diaxial strains, and thus their carbocyclization reactions were facilitated.

To reinforce this mechanistic explanation and confirm the initial hypothesis of an *anti*-carbocupration step,[19] the reaction



Scheme 5 Transition state proposal.

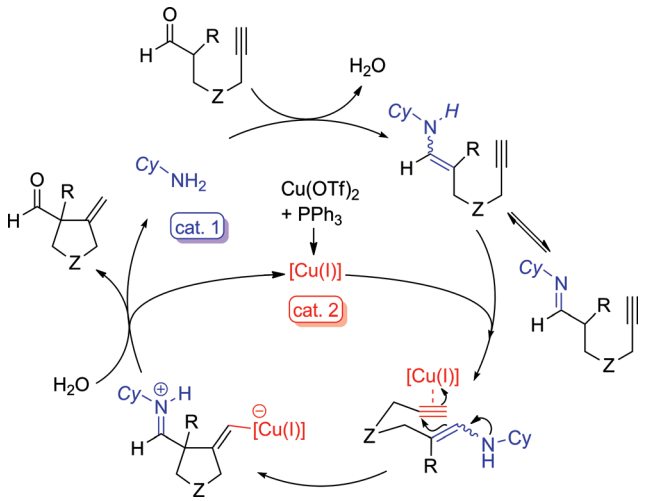


Reaction Conditions: (1 hour, 40% conv.) **A/C/D** ratio
a) 5 mol% $Cu(OTf)_2$, 20 mol% PPh_3, 20 mol% $CyNH_2$ 47/43/10
b) 5 mol% $Cu(OTf)_2$, 20 mol% PPh_3, 100 mol% $CyNH_2$ 38/59/3

Scheme 6 Investigation of the carbocupration stereoselectivity.

was carried out on the deuterium labelled compound **9-D** (Scheme 6). Taking into account the well-known ability of copper(I) to promote the formation of copper acetylides from terminal alkynes, a D–H scrambling could be observed. Therefore this study was realized at incomplete conversion in order to limit this undesired process. At first, the carbocyclization was realized with 5 mol% $Cu(OTf)_2$, 20 mol% PPh_3 and 20 mol% $CyNH_2$ and led to diversely deuterated or non-deuterated carbocycles **A–D**. Analysis of the ^1H NMR spectrum in the ethylenic region of the crude reaction mixture gave the relative ratios of **A**, **C** and **D**,[20] respectively 47%, 43% and 10%. This would imply a predominant *anti*-carbocupration pathway, since the labelled carbocycle **A** was mainly formed during this process (Scheme 5, conditions a). The participation of *syn*-carbocupration could not be fully excluded, considering the presence of a small amount of **D**. Since the formation of **D** could either be rationalized through a *syn*-carbometallation followed by protodemetallation, or, less straightforwardly, could result from a D–H exchange/*anti*-carbocupration/deuterodemetallation pathway, the same experiment was repeated with a stoichiometric amount of cyclohexylamine. The presence of a larger quantity of amine would allow, while acting as a proton source, to distinguish between this two processes since deuterodemetallation should be depressed compared to protodemetallation (Scheme 5, conditions b). Under these reaction conditions, as expected, a higher relative amount of **C** was observed, and more interestingly, the formation of **D** was limited compared to the formation of **A**. Therefore, the formation of **D** probably came from the D–H exchange/*anti*-carbocupration/deuterodemetallation pathway, and thus, in overall, carbocupration occurred in an *anti*-stereoselective manner.

Finally, we propose the following catalytic cycle in which the metallo-organocatalytic process would involve the amine catalyst as accountable for the formation of a nucleophilic enamine (in tautomerism with its imine form), whereas the *in situ* generated copper(I) complex would enhance the electrophilicity of the alkynyl residue. Both activations would then trigger the carbocyclization process through an *anti*-carbocupration pathway



Scheme 7 Proposed metallo-organocatalytic cycle.

following a chair like transition state, and the catalysts would be regenerated by hydrolysis and protodemetallation of the transient iminium vinylcopper accompanied by the liberation of the desired carbocyclized carbaldehyde (Scheme 7).

Conclusions

In summary, we report herein an original metallo-organocatalytic system that combines both the use of catalytic quantities of cyclohexylamine with the use of a copper(I) catalyst. This catalytic system allowed the efficient room temperature carbocyclization reactions of a broad range of α-disubstituted formyl alkynes leading to a high variety of 5-membered cyclic skeletons including cyclopentanes, indanes, pyrrolidines and tetrahydrofuran, in good to excellent yields. Differences in cyclization rates in addition to deuterium labelling experiments tend to suggest a chair like transition state in which an *anti*-stereoselective carbocupration ring closure operates. Further investigations concerning a tandem Michael addition/carbocyclization process, as well as an enantioselective version of this reaction are currently ongoing and will be reported in due course.

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