

Accepted Article

Title: Cyclodextrin cavity-induced mechanistic switch in copper-catalyzed hydroboration

Authors: Pinglu Zhang, Jorge Mejjide Suarez, Thomas Driant, Etienne Derat, Yongmin Zhang, Mickaël Ménand, Sylvain Roland, and Matthieu Sollogoub

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201705303
Angew. Chem. 10.1002/ange.201705303

Link to VoR: <http://dx.doi.org/10.1002/anie.201705303>
<http://dx.doi.org/10.1002/ange.201705303>

Cyclodextrin cavity-induced mechanistic switch in copper-catalyzed hydroboration

Pinglu Zhang, Jorge Meijide Suárez, Thomas Driant, Etienne Derat, Yongmin Zhang, Mickaël Ménand, Sylvain Roland,* Matthieu Sollogoub*[a]

Abstract: NHC-capped cyclodextrin (ICyD) ligands, α -ICyD and β -ICyD derived from α - and β -cyclodextrin respectively give opposite regioselectivities in a copper-catalyzed hydroboration. The site-selectivity results from two different mechanisms: the conventional “parallel” one and a new “orthogonal” mechanism. The shape of the cavity was shown not only to induce a regioselectivity switch but also a mechanistic switch. The scope of interest of the encapsulation of a reactive center is therefore broadened by this study.

Encapsulated metal complexes show distinctive behaviors resulting from the confinement of the metal.^[1] The cavity plays the role of second coordination sphere, which impacts reactivity and selectivity.^[2–7] Alterations in regioselectivity were observed with encapsulated metal catalysts in hydration or hydroformylation reactions.^[8–11] An unusual coordination mode of the complex imposed by the confinement, or a controlled approach of the substrate imposed by sterics have been raised to explain the changes. Hence, regioselectivity is influenced by confinement of the reactive center but the reaction mechanism itself was not invoked. We present here a system in which not only the regioselectivity can be switched by only changing the size of a cavity but also the actual mechanism of the reaction. We also demonstrate another benefit of encapsulation in the discovery of new mechanisms.

In the framework of our studies on cyclodextrin (CD)-based metal catalysts,^[12] we developed *N*-heterocyclic carbene (NHC)-capped CD complexes, called (ICyD)M, where the metal is literally wrapped by the CD scaffold.^[13] The position of an appended metal inside this cavity forces external ligands to be influenced by its shape to interact with the metal center. Thus, these particular structures were found to induce shape-dependent enantio- and regioselectivities in gold-catalyzed cycloisomerisation reactions.^[14] Structural analyses of (α -ICyD)M and (β -ICyD)M complexes, derived from α and β -CD, respectively, revealed significant differences in shape, in particular in the close surroundings of the metal. For instance, α - and β -ICyD-based complexes both present a groove leading to the metal, but for (β -ICyD)M, a pit situated next to the metallic center is observed whereas the metal is tightly wrapped in (α -ICyD)M (Figure 1).^[14] This suggests that a lateral approach to the metal may be conceivable for (β -ICyD)M complexes but precluded for α -ICyD. We therefore wondered if we could rely on those differences to operate site-selective reactions based on

differences of accessibility to the metal.

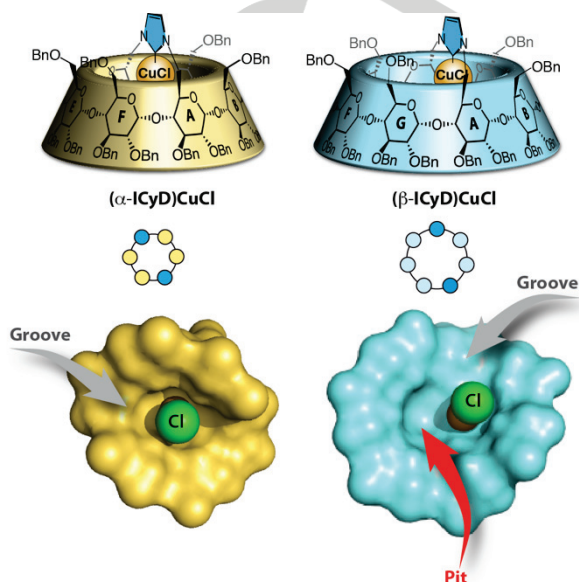


Figure 1. Structures and three-dimensional views of NHC-capped α and β -CD-derived copper(I) complexes.

For some time now, catalytic versions of the copper-mediated borylation of alkynes, using (Bpin)₂ as boryl donor,^[15,16] have been developed.^[17] Remarkably, inversions of regioselectivities have been observed, particularly by introducing different copper ligands.^[18–23] For aryl-substituted terminal alkynes, and with non-bulky ligands, the selectivity is generally in favor of the linear adduct (or β -product, Scheme 1).^[24] An inversion of this trend was observed by Hoveyda with the bulky *N*-aryl NHC ligand SIPr which favored the formation of the branched adduct.^[18] Surprisingly, NHC–copper complexes bearing *N*-alkyl substituted NHCs such as SIAd, of similar steric demand compared to SIPr,^[25] were found to give the opposite regioselectivity, leading to linear products,^[18] and demonstrating that the electronic properties of the NHC ligand may be predominant in controlling the reaction. Therefore, this reaction appeared as a good probe to observe the effect of a cavity, and more particularly of a CD cavity, on regioselectivity.

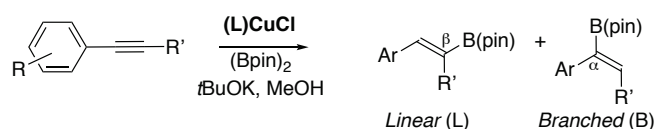
In this study, we compared α - and β -ICyD (Figure 1) of different cavity size but having identical *N*-alkyl-substituents. Much to our delight, the α -CD gave the linear borylated product as the major isomer whereas the β -CD gave the branched one (Scheme 1). Therefore, the α -CD-derived NHC gave similar results than the bulky *N*-alkyl-substituted NHC SIAd, but the result obtained with the β -CD-derived NHC was unexpected for an *N*-alkyl-substituted NHC, suggesting a control by the cavity. Noteworthy, after a round of optimization,^[26] we found that the different

[a] Dr. P. Zhang, J. Meijide Suárez, T. Driant, Dr. E. Derat, Dr. Y. Zhang, Dr. M. Ménand, Dr. S. Roland, Prof. M. Sollogoub

Sorbonne Université, UPMC Univ Paris 06, CNRS
Institut Parisien de Chimie Moléculaire (IPCM), UMR 8232
4, place Jussieu, 75005 Paris, France
E-mail: sylvain.roland@upmc.fr, matthieu.sollogoub@upmc.fr
Homepage: <http://www.ipcm.fr/Presentation,293>

Supporting information for this article is given via a link at the end of the document.

experimental conditions to get Linear (RT) or Branched (-20°C) derivatives described by Hoveyda were also the most efficient in our case.^[18] We then operated a review of various electronic effects on the alkyne aryl group in all *ortho*, *meta* and *para* positions. (α -ICyD)CuCl consistently gave the linear product whereas (β -ICyD)CuCl gave the branched compound as the major one. In the case of (β -ICyD)CuCl, a notable drop of regioselectivity is observed with methyl or OMe, *ortho*- and *meta*-substituted phenylacetylenes, suggesting that sterics of the substrate affects the regioselective outcome of the reaction. (α -ICyD)CuCl and (β -ICyD)CuCl gave also contrasted results with internal non-symmetrical alkynes. In the case of the α -CD-based catalyst, the selectivity remains in favor of the linear (β -) compound regardless of the Me or Et alkyl group linked to the alkyne. In contrast, for the β -CD-based catalyst, increasing of the R group size erodes the regioselectivity in favor of the branched (α -) compound and an inversion of selectivity was observed for the Et-derived phenylacetylene.

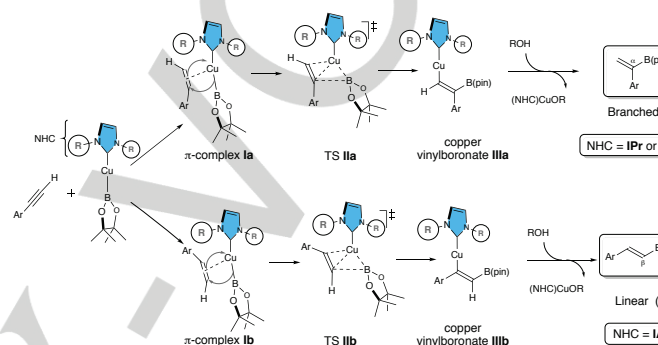


R	R'	Product	Yield	L:B ratio	Yield	L:B ratio
			(α -ICyD)CuCl at RT		(β -ICyD)CuCl at -20°C	
H	H	1	63%	91:9	71%	10:90
<i>p</i> -MeO	H	2	67%	93:7	87%	10:90
<i>m</i> -MeO	H	3	71%	94:6	82%	12:88
<i>o</i> -MeO	H	4	55%	93:7	64%	46:54
<i>p</i> -Me	H	5	49%	92:8	66%	8:92
<i>m</i> -Me	H	6	48%	93:7	78%	14:86
<i>o</i> -Me	H	7	39%	93:7	74%	19:81
<i>p</i> -Cl	H	8	61%	95:5	25%	9:91
<i>m</i> -Cl	H	9	70%	97:3	40%	6:94
<i>o</i> -Cl	H	10	68%	94:6	68%	9:91
<i>p</i> -F	H	11	48%	86:14	65%	4:96
<i>m</i> -F	H	12	65%	95:5	55%	5:95
<i>o</i> -F	H	13	45%	92:8	67%	7:93
<i>p</i> -CF ₃	H	14	64%	98:2	30%	2:98
<i>m</i> -CF ₃	H	15	63%	86:14	48%	4:96
<i>o</i> -CF ₃	H	16	55%	91:9	44%	10:90
H	Me	17	54%	92:8	72%	37:63
H	Et	18	25%	90:10	65%	64:36

Scheme 1. Model reaction to study the regioselectivity induced by the CD cavity. (L) = CD-NHC ligands α -ICyD or β -ICyD.

The copper-mediated borylation of alkynes is thought to start with activation of the (L)CuCl pre-catalyst by *t*BuOK to form a (L)Cu–OtBu adduct which reacts with (BPin)₂ to give a (L)Cu–Bpin complex.^[15–18,27,28] Next, the formation of a vinyl copper species resulting from concerted *syn* borylcupration of the alkyne was proposed.^[29] The regioselectivity of the reaction is influenced at this step both by the initial approach of the alkyne on the copper atom to form the π -complex (**1a** or **1b** Scheme 2) and by the TS (**1Ia** or **1Ib**) of the insertion step. This "parallel" lateral approach of the alkyne to the NHC–Cu–B bond was extensively investigated by theoretical calculations.^[18,30] Generally, less hindered and more electronically rich ligands

favor linear product formation, whereas more sterically hindered less electron-donating ligands give branched products. However, this last statement seems to be in contradiction with our results, as the most sterically hindered ligand α -ICyD affords linear products, when the larger β -CD derivative favors branched compounds. NMR analyses of all (L)CuCl, (L)Cu–OtBu, and (L)Cu–Bpin intermediates for both α -ICyD and β -ICyD ligands (see SI), showed deshielding of H-5s characteristic of the metal inside the cavity.^[13,14] This demonstrates that the *syn* borylcupration step, which controls regioselectivity, is forced to take place inside the cavity with (ICyD)CuBpin intermediates.



Scheme 2. Proposed pathways for the formation of the branched or linear adducts with (NHC)CuCl.

We found next by molecular modeling using DFT calculations (see SI) that the alkyne can only access the copper atom of (β -ICyD)CuBpin when the phenyl group is positioned next to the entrance of the cavity to form π -complex **1a**. (Scheme 2 and Figure 2). Therefore, the approach of phenylacetylene is clearly governed by the shape of the cavity that imposes a reverse approach compared to the reported *N*-alkyl-substituted NHCs, and overrules the electronic effects, resulting in high selectivity for the branched isomer. This is consistent with the low sensitivity of the reaction to the electronic effects of the Ar substituents but rather to their steric hindrance (Scheme 1).

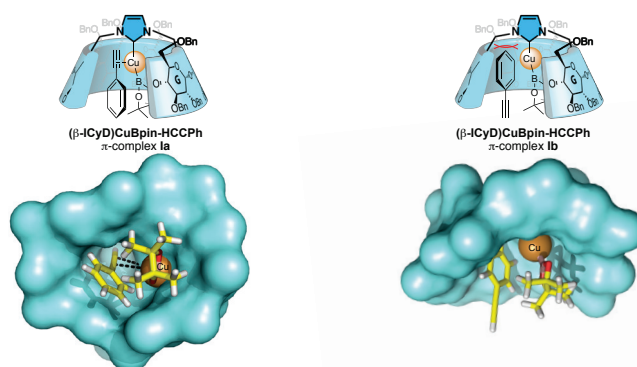
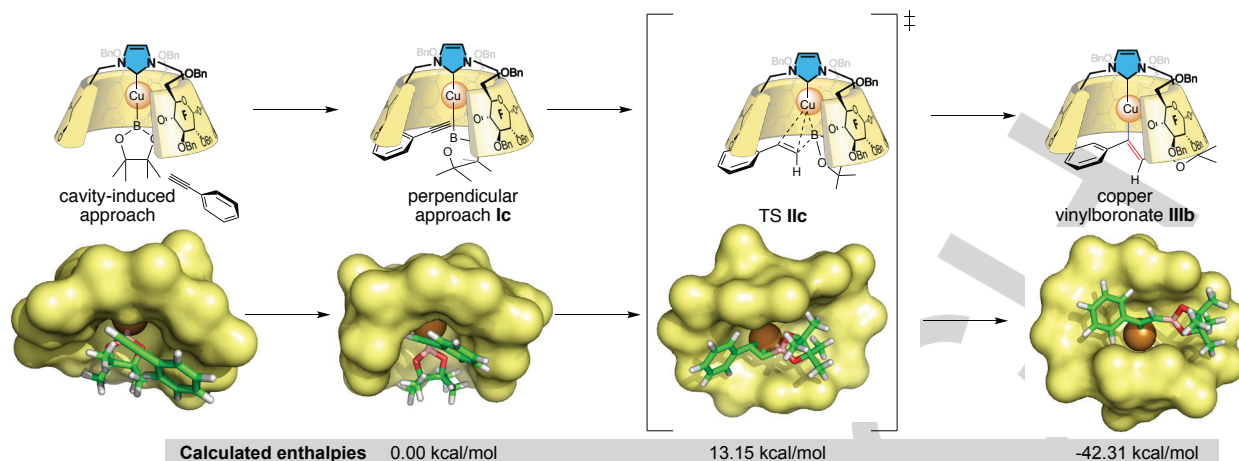


Figure 2. DFT Modeling of the two possible parallel approaches of phenylacetylene to the Ccarbene–Cu–B bond with (β -ICyD)CuBpin. In the right approach with the phenyl group inside the cavity (π -complex **1b**), the alkyne cannot reach the reactive copper center.

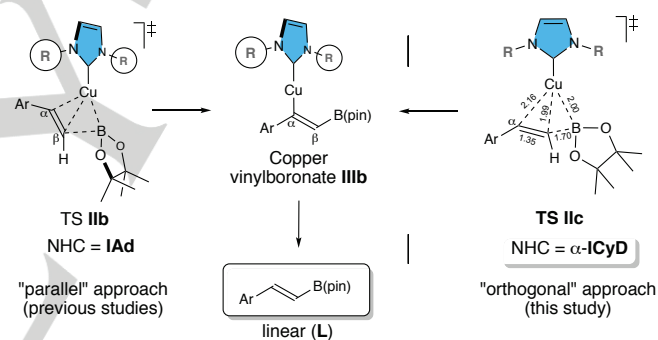


Scheme 3. Proposed "orthogonal" mechanism for the borylation reaction with α -ICyD with the corresponding calculated enthalpies.

The results obtained with α -ICyD are therefore puzzling, as, when considering the "parallel" approach, formation of the linear product would imply an inclusion of the phenyl in the cavity deep enough to bring the triple bond next to the copper atom to form **1b**. This approach that was sterically unfavorable with the wider β -ICyD, is even more difficult to conceive with the tighter α -ICyD. In fact, our initial attempts to theoretically study the mechanism failed. By trying to approach the alkyne towards the metal, we observed that the steric hindrance around the copper atom clearly prevented alkyne coordination. We therefore changed our strategy and decided to operate a backward study. We assumed that the alkenylcopper intermediate (**1llb**) was formed and modeled it. Then, we imposed an iterative shortening of the Cu-B bond. In doing so, we were able to observe the passage through a transition state involving coordination of the metal center with the boron atom and both carbons involved. Further reduction of the Cu-B distance resulted in the release of the alkyne and revealed an original quasi-perpendicular approach at the level of the Cu-B bond (**1c** in Scheme 3). The confinement of the metal center inside the cavity of α -ICyD therefore not only induces a switch of regioselectivity but also of mechanism from "parallel" to "orthogonal" (Schemes 3 and 4).

To explain the regioselectivity of the reaction, we examined in detail the inter-atomic distances in the corresponding **TS 1lc**. It appears that the B-C β bond is rather short (1.70 Å) whereas the C α -Cu bond is long (2.16 Å). This observation implies the development of a negative charge at C α . The regioselectivity in favor of the Linear product is therefore probably governed by the development of this negative charge which is stabilized by the phenyl (Scheme 4).^[27] In light of the two mechanisms proposed here, it is also possible to rationalize the results obtained with internal alkynes. For α -ICyD the mechanism remains the same and the linear product is still the major one, although the yield decreases probably due to steric hindrance preventing access to the metal. The regioselectivity in favor of the attachment of the boron atom next to the alkyl chain rather than next to the phenyl group can also be accounted for in light of the proposed transition state (**TS 1lc**). Indeed, the development of a negative charge is more stabilized by a phenyl than an alkyl group.^[27] In the case of β -ICyD, the adjunction of a methyl and *a fortiori* an ethyl group on the alkyne makes the triple bond less accessible to the metal in the case of the "parallel" mechanism. In this case

the competitive "orthogonal" mechanism leading to the linear product for the same electronic reasons as for α -ICyD can be considered. We therefore propose that a switch in mechanism from "parallel" to "orthogonal" in the β -ICyD case explains the reversal of regioselectivity from branched to linear for hindered internal alkynes.



Scheme 4. Mechanistic switch from "parallel" to "orthogonal" imposed by the cavity.

We showed that ICyD ligands could be used for regioselective copper-catalyzed hydroboration. The outcome of the reaction is governed by the nature of the CD, α -CD giving the Linear product, while β -CD derivative gives the Branched product with terminal alkynes. In fact, it is the difference in shape of those two catalysts that imposes the site-selectivity, which results from two different mechanisms: the conventional "parallel" mechanism and a new one uncovered by this study, a so-called, "orthogonal" mechanism. In this particular case, the shape of the cavity not only induces a regioselectivity switch but also a mechanistic switch.^[31] Furthermore, the orthogonal approach is a new mechanistic proposal for this reaction that might be considered in other cases, for example for the reaction operated on a metallic copper surface where the metal center is also hindered.^[32] The scope of interest of the encapsulation of a reactive center was broadened here, as it revealed a different mechanism in a well-studied reaction, a feature that probably exists in other systems.

Acknowledgements

MS thanks Professor Amir Hoveyda for a fruitful discussion that led to this work. PZ thanks the CSC for PhD grant. ED thanks Sven Klumpe for preliminary investigations on the mechanism. The authors thank LabEx *MiChem* part of French state funds managed by the ANR within the Investissements d'Avenir programme under reference ANR-11-IDEX-0004-02, Cyclolab (Hungary) and Roquette (France) for generous supply of α - and β -CDs respectively.

Keywords: Cyclodextrins, Metallo-pockets; Molecular shape; Cavity; N-heterocyclic carbenes (NHC); Catalysis

- [1] M. Raynal, P. Ballester, A. Vidal-Ferran, P. W. N. M. Van Leeuwen, *Chem. Soc. Rev.* **2014**, 43, 1734; C. J. Brown, F. D. Toste, R. G. Bergman, K. N. Raymond, *Chem. Rev.* **2015**, 115, 3012; S. H. A. M. Leenders, R. Gramage-Doria, B. de Bruin, J. N. H. Reek, *Chem. Soc. Rev.* **2015**, 44, 433
- [2] M. A. Sarmentero, H. Fernandez-Pérez, E. Zuidema, C. Bo, A. Vidal-Ferran, P. Ballester, *Angew. Chem. Int. Ed.* **2010**, 49, 7489
- [3] Z. J. Wang, C. J. Brown, R. G. Bergman, K. N. Raymond, F. D. Toste, *J. Am. Chem. Soc.* **2011**, 133, 7358
- [4] C. Gibson, J. Rebek, *Org. Lett.* **2002**, 4, 1887; P. F. Kuijpers, M. Otte, M. Dürr, I. Ivanovic-Burmazovic, J. N. H. Reek, B. de Bruin, *ACS Catal.* **2016**, 6, 3106; M. Otte, *ACS Catal.* **2016**, 6, 6491
- [5] A. C. H. Jans, A. Gómez-Suárez, S. P. Nolan, J. N. H. Reek, *Chem. Eur. J.* **2016**, 22, 14836
- [6] C. Zhao, Q.-F. Sun, W. M. Hart-Cooper, A. G. DiPasquale, F. D. Toste, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2013**, 135, 18802
- [7] D. Zhang, K. Jamieson, L. Guy, G. Gao, J.-P. Dutasta, A. Martinez, *Chem. Sci.* **2017**, 8, 789
- [8] A. Cavarzan, A. Scarso, P. Sgarbossa, G. Strukul, J. N. H. Reek, *J. Am. Chem. Soc.* **2011**, 133, 2848
- [9] V. Bocokic, A. Kalkan, M. Lutz, A. L. Spek, D. T. Gryko, J. N. H. Reek, *Nat. Commun.*, **2013**, 4, 2670
- [10] C. García-Simón, R. Gramage-Doria, S. Raoüfoghaddam, T. Parella, M. Costas, X. Ribas, J. N. H. Reek, *J. Am. Chem. Soc.* **2015**, 137, 2680
- [11] M. Jouffroy, R. Gramage-Doria, D. Armspach, D. Sémeril, W. Oberhauser, D. Matt, L. Toupet, *Angew. Chem., Int. Ed.* **2014**, 53, 3937
- [12] S. Guieu, E. Zaborova, Y. Blériot, G. Poli, A. Jutand, D. Madec, G. Prestat, M. Sollogoub, *Angew. Chem. Int. Ed.* **2010**, 49, 2314; E. Zaborova, J. Deschamp, S. Guieu, Y. Blériot, G. Poli, M. Ménand, D. Madec, G. Prestat, M. Sollogoub, *Chem. Commun.* **2011**, 47, 9206; F.-X. Legrand, M. Ménand, M. Sollogoub, S. Tilloy, E. Monflier, *New J. Chem.* **2011**, 35, 2061; M. Guitet, F. Marcelo, S. Adam de Beaumais, Y. Zhang, J. Jiménez-Barbero, S. Tilloy, E. Monflier, M. Ménand, M. Sollogoub, *Eur. J. Org. Chem.* **2013**, 3691
- [13] M. Guitet, P. Zhang, F. Marcelo, C. Tugny, J. Jiménez-Barbero, O. Buriez, C. Amatore, V. Mouriès-Mansuy, J.-P. Goddard, L. Fensterbank, Y. Zhang, S. Roland, M. Ménand, M. Sollogoub, *Angew. Chem. Int. Ed.* **2013**, 52, 7213
- [14] P. Zhang, C. Tugny, J. Meijide Suárez, M. Guitet, E. Derat, N. Vanthuyne, Y. Zhang, O. Bistri, V. Mouriès-Mansuy, M. Ménand, S. Roland, L. Fensterbank, M. Sollogoub, *Chem* **2017**, 3, 174
- [15] K. Takahashi, T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2001**, 625, 47
- [16] J.-E. Lee, J. Kwon, J. Yun, *Chem. Commun.* **2008**, 733; H. R. Kim, I. G. Jung, K. Yoo, K. Jang, E. S. Lee, J. Yun, S. U. Son, *Chem. Commun.* **2010**, 46, 758; H. R. Kim, J. Yun, *Chem. Commun.* **2011**, 47, 2943
- [17] J. Yun, *Asian J. Org. Chem.* **2013**, 2, 1016; R. Barbeyron, E. Benedetti, J. Cossy, J.-J. Vasseur, S. Arseniyadis, M. Smietana, *Tetrahedron*, **2014**, 70, 8431; T. Fujihara, K. Semba, J. Terao, Y. Tsuji, *Catal. Sci. Technol.* **2014**, 4, 1699; H. Yoshida, *ACS Catal.* **2016**, 6, 1799
- [18] H. Jang, A. R. Zhugralin, Y. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, 133, 7859
- [19] J. K. Park, B. A. Ondrusek, D. T. McQuade, *Org. Lett.* **2012**, 14, 4790
- [20] Y. D. Bidal, F. Lazreg, C. S. J. Cazin, *ACS Catal.* **2014**, 4, 1564
- [21] J. S. da Costa, R. K. Braun, P. A. Horn, D. S. Lüdtkke, A. V. Moro, *RSC Adv.* **2016**, 6, 59935
- [22] W. Su, T.-J. Gong, Q. Zhang, Q. Zhang, B. Xiao, Y. Fu, *ACS Catal.* **2016**, 6, 6417
- [23] Z.-J. Yao, S. Hong, W. Zhanga, M. Liua, W. Deng, *Tetrahedron Lett.* **2016**, 57, 910
- [24] We will use Linear and Branched products instead of a and b products, not to confuse the reader with α - and β -CDs nomenclature.
- [25] A. Poater, B. Cosenza, A. Correa, S. Giudice, F. Ragone, V. Scarano, L. Cavallo, *Eur. J. Inorg. Chem.* **2009**, 1759
- [26] We found that (α -ICyD)CuCl worked well at R.T. At this temperature (β -ICyD)CuCl gave a faster reaction (2 h instead of 12 h) and a 75:25 ratio in favor of the Branched compound. We lowered the reaction temperature to -20°C for this catalyst to obtain a 90:10 ratio. This difference of reactivity is probably linked to the accessibility of the metal in the cavity.
- [27] J. H. Moon, H.-Y. Jung, Y. J. Lee, S. W. Lee, J. Yun, J. Y. Lee, *Organometallics* **2015**, 34, 2151
- [28] D. S. Laitar, P. Müller, J. P. Sadighi, *J. Am. Chem. Soc.* **2005**, 127, 17196
- [29] D. S. Laitar, E. Y. Tsui, J. P. Sadighi, *Organometallics* **2006**, 25, 2405
- [30] J. H. Moon, H.-Y. Jung, Y. J. Lee, S. W. Lee, J. Yun, J. Y. Lee, *Organometallics* **2015**, 34, 2151
- [31] Selected examples: Y. Pocker, B. P. Ronald, *J. Am. Chem. Soc.* **1980**, 102, 5311; M. Chabanas, V. Vidal, C. Copéret, J. Thivolle-Cazat, J.-M. Basset, *Angew. Chem. Int. Ed.* **2000**, 39, 1962; S. Ma, Z. Shi, *Chem. Commun.* **2002**, 540; C. J. Abraham, D. H. Paull, T. Bekele, M. T. Scerba, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **2008**, 130, 17085; M. M. Hansmann, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2013**, 52, 2593; D. Carrasco, M. García-Melchor, J. A. Casares, P. Espinet, *Chem. Commun.* **2016**, 52, 4305
- [32] J. Zhao, Z. Niu, H. Fu, Y. Li, *Chem. Commun.* **2014**, 50, 2058

Entry for the Table of Contents

COMMUNICATION

Pinglu Zhang, Jorge Mejjide Suárez,
Thomas Driant, Etienne Derat, Yongmin
Zhang, Mickaël Ménand, Sylvain
Roland, * Matthieu Sollogoub*

Page No. – Page No.

Cavity-induced mechanistic switch

Cavity switch. NHC-capped cyclodextrin ligands, derived from α - and β -cyclodextrins give opposite regioselectivities in a copper-catalyzed hydroboration. This results from two different mechanisms: the conventional “parallel” one and a new “orthogonal” mechanism. The shape of the cavity was shown to induce both a regioselectivity and a mechanistic switch. The scope of interest of the encapsulation of a reactive center is therefore broadened by this study.

