Organo- and Copper-Multi-Catalyzed Pseudo Four-Component Access to gem -Difluorohydrins

Angela Ricucci, Jean Rodriguez, Adrien Quintard

▶ **To cite this version:**

Angela Ricucci, Jean Rodriguez, Adrien Quintard. Organo- and Copper-Multi-Catalyzed Pseudo Four-Component Access to gem -Difluorohydrins. European Journal of Organic Chemistry, 2018, 2018 (27-28), pp.3697 - 3700. 10.1002/ejoc.201701459 . hal-01850449

HAL Id: hal-01850449
https://hal.science/hal-01850449

Submitted on 27 Jul 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Organo- and Copper-Multi-Catalyzed Pseudo Four-Component Access to *gem*-Difluorohydrins

Angela Ricucci,[a] Jean Rodriguez,[a] and Adrien Quintard*[a]

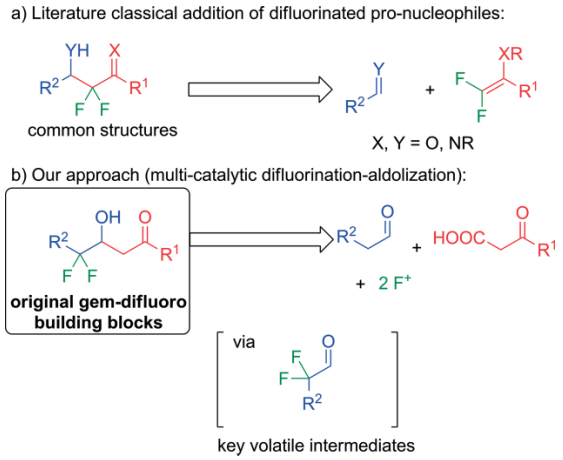
Abstract: A new efficient multi-catalytic pseudo four-component strategy combining an aldehyde, a β-keto-acid and two equivalents of a fluorinating agent has been designed. Thanks to the combined effects of a secondary amine as organocatalyst and a copper catalyst, highly volatile *gem*-difluorinated intermediates can be produced and trapped in situ by a chemo-compatible decarboxylative aldolization providing a rapid access to original *gem*-difluorinated β-aldol building blocks.

Introduction

The eco-compatible construction of original molecular scaffolds occupying unexplored space of the chemical map is crucial if chemists want to continue developing medical treatments with increased efficiency. In this context, the rapid and selective insertion of *gem*-difluorinated elements into innovative structures is of great expectation in order to obtain potential drugs with optimized biological profiles. In addition to the well-studied CF and CF_3 groups, insertion of the *gem*-difluoro unit has been shown to be highly beneficial in drug design,[1] thanks to the intrinsic properties of the fluorine atom known notably to modulate lipophilicity, acidity, or conformational properties.[2] As a result, the introduction of the CF_2 group was shown to confer improved bioactivity to numerous drug scaffolds.

One of the most common approaches of accessing *gem*-difluorinated molecules with adjacent functional groups such as alcohols or amines, other than the bis-fluorination of 1,3-dicarbonyl compounds,[3] relies on the use of *gem*-difluorinated pronucleophiles (Scheme 1 a).[4] Indeed, by taking advantage of the electronic properties conferred by the presence of the CF_2 substituent, nucleophilic additions of various difluorinated pronucleophiles to imines, aldehydes or ketones were performed.[5]

Quite surprisingly, excluding the nucleophilic aldolization of electronically biased aldehydes containing a perfluoroalkyl chain,[6] the alternative direct aldolization to *gem*-difluorinated aldehydes is to the best of our knowledge unprecedented. This lack of literature development is due to the high volatility of the required fluorinated aldehydes. Because of this particular physical property, the direct access to the original alternative building blocks proposed in Scheme 1 b would require the identification of a one-pot process that allows the in situ formation of the required *gem*-difluoro aldehyde, potentially by



Scheme 1. Proposed approach to original *gem*-difluorohydrins.

enamine activation,[7] combined with a chemo-compatible decarboxylative aldolization, resulting in the otherwise difficult C–C bond formation.

Herein, we report our findings on the development of a one-pot organo- and copper-catalyzed pseudo four-component combination of a fluorine source, aliphatic aldehydes and keto-acids.[8] This eco-compatible strategy allows the rapid and easy formation of original *gem*-difluorinated β-aldols featuring great potential to serve as valuable building blocks for medicinal chemistry.

Results and Discussion

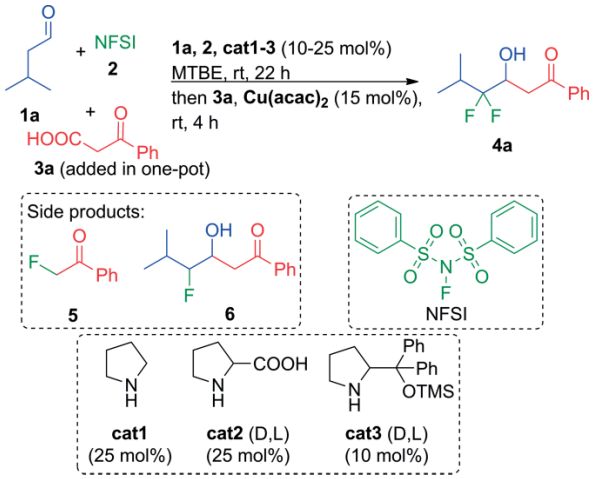
In order to develop the designed multi-component reaction, we focused our attention on the use of different secondary amines to promote the bis-fluorination of aliphatic aldehydes in the most reliable manner by an enamine type organocatalytic activation.[7] A copper-catalyzed decarboxylative aldolization using keto-acids was selected to trap in-situ the generated *gem*-difluoro aldehydes due to the high reactivity and compatibility

[a] *Aix Marseille Université, CNRS, Centrale Marseille, iSm2, Marseille, 13397, France*
E-mail: adrien.quintard@univ-amu.fr
http://ism2.univ-amu.fr/fr/stereo/stereo

of this aldolization system generating only one molecule of CO_2 as waste.[9,10]

We first focused our attention on the use of inexpensive pyrrolidine **cat1** or (D,L)-proline **cat2** to catalyze the bis-fluorination of isovaleraldehyde **1a**. These two molecules were described in the literature to promote the bis-fluorination of aldehydes albeit using protic solvents or very high catalyst loading.[7] Unfortunately, the use of a protic solvent (*i*PrOH) was detrimental for the sequence providing **4a** only in trace amount (Table 1, entries 1 and 2). Turning to the use of a non-protic solvent optimal for the aldolization such as MTBE (*tert*-butyl-methyl ether) considerably limited the formation of the bis-fluorinated aldehyde to lower than 20 % (Table 1, entries 3–4). These disappointing results led us turn out our attention to the use of racemic diphenyl-prolinol silyl ether **cat3** previously used for the selective bis-fluorination of aldehydes.[7c]

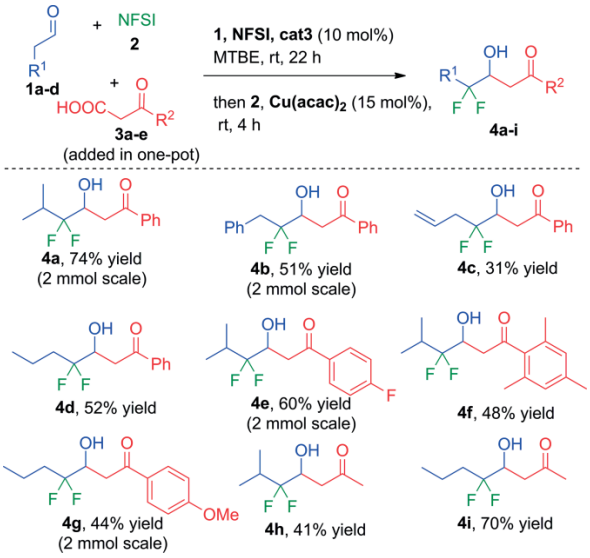
Table 1. Optimization of the multi-catalyzed bis-fluorination/aldolization.



Entry	cat	Solvent	**2** (Equiv.)	Result
1	cat1	*i*PrOH/THF	2.5	Traces
2	cat2	*i*PrOH/THF	2.5	Traces
3	cat1	MTBE	2.5	Bis-fluorinated aldehyde formation < 20 %
4	cat2	MTBE	2.5	Bis-fluorinated aldehyde formation < 20 %
5	cat3	MTBE	2.5	Full conv, purified compound contains **5**
6	cat3	MTBE	1.9	Full conv, purified compound contains **6**
7	**cat3**	**MTBE**	**2.0**	74 % isolated yield

It is important to note that the use of the racemic catalyst is of utmost importance for the formation of the bis-fluorinated aldehyde. Indeed, if the enantiopure catalyst is used, the formation of an enantioenriched configurationally stable enough mono-fluorinated aldehyde precludes the subsequent enamine formation with the same enantiomer of the catalyst, thus avoiding the bis-fluorination.[11] Fortunately, using this catalyst, the multi-component reaction did provide access to the expected product **4a**. However, using un-optimized conditions (entries 5–6), notably with 2.5 or 1.9 equiv. of NFSI (*N*-fluorobenzenesulfonamide), formation of the side products **5** or **6** of close polarity with **4a** did not allow the isolation of the expected product in its pure form. However, using the exact combination between 1 equiv. of aldehyde and 2 equiv. of the fluorine source simplified the purification, gratifyingly providing the clean **4a** in 74 % isolated yield (Entry 7).

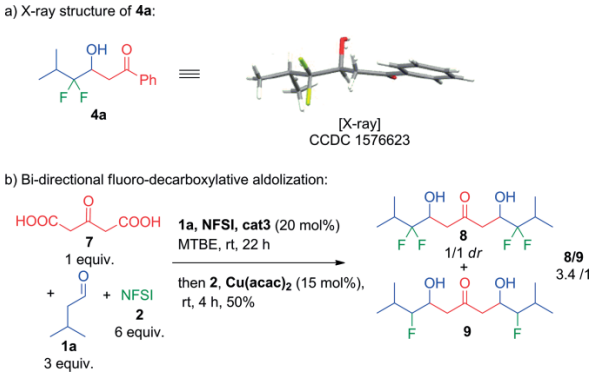
With these optimized conditions in hand, the multi-catalyzed synthesis of variously substituted *gem*-difluorinated compounds was undertaken (Scheme 2). As a general trend, structurally diverse *gem*-difluorinated adducts can be prepared from aldehydes possessing branched or linear alkyl chains (**4a**, **4d**–**i**), aromatic subsitutent (**4b**) or terminal alkene (**4c**). The keto-acid **3a** can be replaced successfully with other pro-nucleophiles containing different aromatic substituents such as 4-F (**4e**), 2,4,6-Me (**4f**) or 4-OMe (**4g**) as well as aliphatic ketones (**4h** and **4i**). In all cases, the reaction is chemically efficient (major formation of **4**), albeit the differences in yields observed between the different products (from 31 to 74 % yield) arise from the difficulty at separating the desired product from the minor impurities in some cases. Despite this limited drawback, the process allows the rapid preparation of a wide array of structurally interesting *gem*-difluorinated compounds.



Scheme 2. Scope of the multi-catalyzed bis-fluorination/aldolization.

Confirming the structure of the multi-component reaction product, X-ray analysis of a co-crystal obtained from a mixture of mono-fluorinated product **6** and bis-fluorinated product **4a** obtained under un-optimized conditions gave a better appreciation of the conformation of the *gem*-difluorinated adduct. (Scheme 3 a).[12] The crystal structure reveals that one of the fluorine atoms is placed in an *anti*-orientation to the alcohol (175°), whereas the other adopted a gauche conformation with the alcohol (63°).[13]

Finally, in order to maximize the complexity generated in a single pot, an attempt was performed to promote a fluoro bi-directional decarboxylative aldolization (Scheme 3 b).[8,10a] This bi-directional approach requires the formation of an excess of bis-fluorinated aldehyde to efficiently promote the subsequent C–C bond-forming reaction. Although this sequence implies the formation of 6 new bonds (4 C–F and two C–C), the complex



Scheme 3. X-ray analysis of **4a** and bi-directional aldolization.

β,β′-keto-diol **8** could be formed through multi-catalysis. However, this reaction also highlights the limits of the fluorination since the bis-fluorination product **8** was obtained together with the known mono-fluorination **9**. This selectivity implies that the minor amount of mono-fluorinated aldehyde formed upon the first part of the sequence reacts faster than the bis-fluorinated aldehyde in the subsequent bi-directional aldolization.

Conclusions

In conclusion, we have developed a new multi-catalyzed one-pot synthesis of original *gem*-difluorohydrins. This sequence involves the organocatalyzed generation of volatile bis-fluorinated aldehydes combined with a chemo-compatible selective copper-catalyzed decarboxylative aldolization. This simple pseudo four-component sequence, occurring with widely available catalysts and starting materials, provides a rapid route to interesting bis-fluorinated building blocks. Given the potential of such molecules for biological studies, future work should focus on the development of an enantioselective version of this transformation,[10] or on the kinetic resolution of the obtained adducts.[14]

Acknowledgments

The Centre National de la Recherche Scientifique (CNRS) and the Aix-Marseille Université (AMU), the Agence Nationale pour la Recherche (ANR-13-PDOC-0007-01), are gratefully acknowledged for financial support. The authors warmly thank Michel Giorgi (Aix-Marseille Université-CNRS) for X-ray analysis.

Keywords: Fluorinated compounds · Fluorine · Organocatalysis · Copper catalysis · Multi-component

[1] For the importance of CF_2 group on drug design see for examples: a) M. Blackburn, D. A. England, F. Kolkmann, *J. Chem. Soc., Chem. Commun.* **1981**, 930; b) M. H. Gelb, J. P. Svaren, R. H. Abeles, *Biochemistry* **1985**, *24*, 1813; c) M. H. Gelb, *J. Am. Chem. Soc.* **1986**, *108*, 3146; d) K. Nakayama, H. C. Kawato, H. Inagaki, R. Nakajima, A. Kitamura, K. Someya, T. Ohta, *Org. Lett.* **2000**, *2*, 977; e) M. Perros, D. A. Price, B. L. C. Stammen, A. Wood, PCT Int. *Appl.* WO2001090106, **2001**; f) A. M. Vignola, *Respir. Med.* **2004**, *98*, 495; g) E. De Clercq, *J. Med. Chem.* **2005**, *48*, 1297; h) D. A. Price, S. Gayton, M. D. Selby, J. Ahman, S. Haycock-Lewandowski, B. L. Stammen, A. Warren, *Tetrahedron Lett.* **2005**, *46*, 5005; i) A. Wood, D. Armour, *Prog. Med. Chem.* **2005**, *43*, 239; j) T. Hakogi, T. Yamamoto, S. Fujii, K. Ikedan, S. Katsumura, *Tetrahedron Lett.* **2006**, *47*, 2627; k) Z. Wang, L. Cheng, Z. Kai, F. Wu, Z. Liu, M. Cai, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3869; l) E. J. Miller, S. G. Mays, M. T. Baillie, R. B. Howard, D. G. Culver, M. Saindane, S. T. Pruett, J. J. Holt, D. S. Menaldino, T. J. Evers, G. P. Reddy, R. F. Arrendale, M. G. Natchus, J. A. Petros, D. C. Liotta, *ACS Med. Chem. Lett.* **2016**, *7*, 537.

[2] a) K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; c) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308; d) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432.

[3] a) C. E. Inman, R. E. Oesterling, E. A. Tyczkowski, *J. Am. Chem. Soc.* **1958**, *80*, 6533; b) S. Stavber, B. Sket, B. Zajc, M. Zupan, *Tetrahedron* **1989**, *45*, 6003; c) R. E. Banks, N. J. Lawrence, A. L. Popplewell, *J. Chem. Soc., Chem. Commun.* **1994**, 343; d) T. Umemoto, M. Nagayoshi, K. Adachi, G. Tomizawa, *J. Org. Chem.* **1998**, *63*, 3379; e) G. Stavber, M. Zupan, M. Jereb, S. Stavber, *Org. Lett.* **2004**, *6*, 4973; f) W. Peng, J. M. Shreeve, *J. Org. Chem.* **2005**, *70*, 5760.

[4] M. Decostanzi, J.-M. Campagne, E. Leclerc, *Org. Biomol. Chem.* **2015**, *13*, 7351.

[5] For selected recent examples in the catalytic enantioselective series see: a) C. Han, E. H. Kim, D. A. Colby, *J. Am. Chem. Soc.* **2011**, *133*, 5802; b) W. Kashikura, K. Mori, T. Akiyama, *Org. Lett.* **2011**, *13*, 1860; c) Z. Yuan, L. Mei, Y. Wei, M. Shi, P. V. Kattamuri, P. McDowell, G. Li, *Org. Biomol. Chem.* **2012**, *10*, 2509; d) Y.-L. Liu, J. Zhou, *Chem. Commun.* **2012**, *48*, 1919; e) P. Zhang, C. Wolf, *Angew. Chem. Int. Ed.* **2013**, *52*, 7869; *Angew. Chem.* **2013**, *125*, 8023; f) J. Qian, W. Yi, X. Huang, J. P. Jasinski, W. Zhan, *Adv. Synth. Catal.* **2016**, *358*, 2811; g) R. Doi, M. Ohashi, S. Ogoshi, *Angew. Chem. Int. Ed.* **2016**, *55*, 341; *Angew. Chem.* **2016**, *128*, 349. For a complete description see: A. Honraedt, A. Van Der Lee, J.-M. Campagne, E. Leclerc, *Adv. Synth. Catal.* **2017**, *359*, 2815 and references cited herein.

[6] a) W. Wang, Q.-Y. Chen, Y. Guo, *Synlett* **2011**, *18*, 2705; For example on ketones possessing adjacent CF_2X chains: b) N. Hara, R. Tamura, Y. Funahashi, S. Nakamura, *Org. Lett.* **2011**, *13*, 1662; c) C. G. Kokotos, *J. Org. Chem.* **2012**, *77*, 1131.

[7] For bis-fluorination of aldehydes via enamine activation see: a) O. O. Fadeyi, C. W. Lindsley, *Org. Lett.* **2009**, *11*, 943; b) S. Harper, M. Ferrara, B. Crescenzi, M. Pompei, M. C. Palumbi, J. M. DiMuzio, M. Donghi, F. Fiore, U. Koch, N. J. Liverton, S. Pesci, A. Petrocchi, M. Rowley, V. Summa, C. Gardelli, *J. Med. Chem.* **2009**, *52*, 4820; c) J. H. Jones, C. Appayee, S. E. Brenner-Moyer, *Eur. J. Org. Chem.* **2014**, 5273; d) A. S. Altiti, S. Bachan, W. Alrowhani, D. R. Mootoo, *Org. Biomol. Chem.* **2015**, *13*, 10328; For other catalytic enamine activation methods used for aldehyde fluorination: e) M. Marigo, D. Fielenbach, A. Braunton, A. Kjaersgaard, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 3703; *Angew. Chem.* **2005**, *117*, 3769; f) T. D. Beeson, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 8826; g) D. Enders, M. R. M. Hüttl, *Synlett* **2005**, 991; h) D. D. Steiner, N. Mase, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2005**, *44*, 3706; *Angew. Chem.* **2005**, *117*, 3772. For other cascades or one-pot reactions based on aldehyde fluorination: i) Y. Huang, A. Walji, M. C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051; j) H. Jiang, A. Falcicchio, K. Jensen, M. W. Paixao, S. Bertelsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2009**, *131*, 7153; k) C. Appayee, S. E. Brenner-Moyer, *Org. Lett.* **2010**, *12*, 3356.

[8] A. Quintard, J. Rodriguez, *ACS Catal.* **2017**, *7*, 5513.

[9] For reviews see: a) Y. Pan, C.-H. Tan, *Synthesis* **2011**, *13*, 2044; b) Z. L. Wang, *Adv. Synth. Catal.* **2013**, *355*, 2745; c) S. Nakamura, *Org. Biomol. Chem.* **2014**, *12*, 394.

[10] For selected examples of catalytic decarboxylative aldolizations: Using organocatalysis: J. Saadi, H. Wennemers, *Nat. Chem.* **2016**, *8*, 276; a) K. Rohr, R. Mahrwald, *Org. Lett.* **2011**, *13*, 1878; b) Y. Zheng, H. Y. Xiong, J. Nie, M. Q. Hua, J. A. Ma, *Chem. Commun.* **2012**, *48*, 4308; c) F. Zhong, W. Yao, X. Dou, Y. Lu, *Org. Lett.* **2012**, *14*, 4018; d) H. Y. Bae, J. H. Sim, J. W. Lee, B. List, C. E. Song, *Angew. Chem. Int. Ed.* **2013**, *52*, 12143; *Angew. Chem.* **2013**, *125*, 12365. Using metal catalysis: e) G. Lalic, A. D. Aloise, M. D. Shair, *J. Am. Chem. Soc.* **2003**, *125*, 2852; f) S. Orlandi, M. Benaglia, F. Cozzi, *Tetrahedron Lett.* **2004**, *45*, 1747; g) D. Magdziak, G. Lalic, H. M.

Lee, K. C. Fortner, A. D. Aloise, M. D. Shair, *J. Am. Chem. Soc.* **2005**, *127*, 7284; h) K. C. Fortner, M. D. Shair, *J. Am. Chem. Soc.* **2007**, *129*, 1032; i) L. Yin, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 9610; j) H.-Y. Xiong, Z.-Y. Yang, Z. Chen, J.-L. Zeng, J. Nie, J.-A. Ma, *Chem. Eur. J.* **2014**, *20*, 8325; k) A. Quintard, J. Rodriguez, *Chem. Eur. J.* **2015**, *21*, 14717; l) A. Quintard, J. Rodriguez, *Chem. Commun.* **2015**, *51*, 9523.

[11] J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296.

[12] CCDC 1576623 (for **4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[13] For a recent comprehensive review on gauche effect: C. Thiehoff, Y. P. Rey, R. Gilmour, *Isr. J. Chem.* **2017**, *57*, 92.

[14] a) T. Tsukamoto, T. Yamazaki, T. Kitazume, *Synth. Commun.* **1990**, *20*, 3181; b) M. Kirihara, M. Kawasaki, H. Katsumata, H. Kakuda, M. Shiro, S. Kawabata, *Tetrahedron: Asymmetry* **2002**, *13*, 2283; c) T. Ema, T. Kadoya, K. Akihara, T. Sakai, *J. Mol. Catal. B* **2010**, *66*, 198.