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## Atom-economical synthesis of 3,3,3trifluoropropanal dialkyl acetals through Pd/C catalyzed acetalization of 3,3,3-trifluoropropene†

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A facile and efficient procedure for one-step synthesis of 3,3,3-trifluoropropanal dialkyl acetals from readily available 3,3,3-trifluoropropene (TFP) has been developed. The catalyst can be recycled for 4 times without obvious deactivation. This process provides a novel and atom-economical synthetic strategy for the preparation of functional CF<sub>3</sub>-containing compounds.

Trifluoromethylated compounds have shown important applications in pharmaceutical chemistry,<sup>1</sup> agrochemistry,<sup>2</sup> and materials science<sup>3</sup> due to their unique chemical and biological properties.<sup>4</sup> Great efforts have been made to develop useful methods for introducing the CF<sub>3</sub> group into organic compounds.<sup>5</sup> The building block approach is considered to be a practical and powerful tool.<sup>6</sup> Therefore, the development of diverse CF<sub>3</sub>-containing building blocks is highly desirable. Meanwhile, the 3,3,3-trifluoropropanal dialkyl acetals are important CF<sub>3</sub>-containing building blocks for 3,3,3-trifluoropropanoic acid, alkyl-3,3,3-trifluoropropionate,<sup>7</sup> and  $\beta$ -CF<sub>3</sub> alcohols.<sup>8</sup>

Several research groups had reported the synthesis of 3,3,3trifluoropropanal dialkyl acetals.<sup>7-9</sup> However, their two-step methods using expensive 1-chloro-3,3,3-trifluoropropene<sup>7</sup> or 2-bromo-3,3,3-trifluoropropene<sup>9</sup> as a starting material have restricted the synthetic application. A more convenient synthetic method involving fewer steps and the readily available starting materials is highly desired.

Acetalization reaction of alkene is a powerful method for the synthesis of acetals in a short sequence. Hosokawa<sup>10</sup> and Jiang<sup>11</sup> reported the acetalization of acrylates by the use of Pd<sup>II</sup> species. Ishii *et al.*<sup>12</sup> reported the acetalization of acrylates catalyzed by Pd(OAc)<sub>2</sub>/NPMoV supported on active carbon. Recently,

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Li *et al.*<sup>13</sup> reported the synthesis of alkyl-3,3-dialkoxypropionates by the acetalization of acrylates using a nanosized CS–Fe<sub>3</sub>O<sub>4</sub>–Pd catalyst. The facile formation of 3,3,3-trifluoropropanal dialkyl acetals *via* the acetalization of alkene is expected. Trifluoropropene (TFP), as an important fundamental building block, is commercially available and its functionalizations *e.g.*, addition reaction,<sup>14</sup> polymerization,<sup>15</sup> hydroformylation<sup>16</sup> and hydroboration<sup>17</sup> have been studied. However, the acetalization of TFP has not been reported so far, presumably due to the fact that TFP is gas at room temperature.

Here we firstly report a convenient and efficient method for one-step preparing 3,3,3-trifluoropropanal dialkyl acetals by the acetalization of TFP with various alcohols using heterogeneous Pd/C–CuCl<sub>2</sub> system (Scheme 1).

Initially, we tried to seek an effective system for the Pd/C catalyzed acetalization of TFP to produce 3,3,3-tri-fluoropropanal dimethyl acetals (**3a**) with O<sub>2</sub> as the oxidant. The effects of different solvents on yield of reaction were investigated including DMF, PEG400, toluene, THF, MeCN and MeOH (Table 1, entries 1–6). The results revealed that the solvent was critical for the success of this reaction because the gas material TFP should be dissolved in the solvent firstly before reaction.

a) previous work



b) this work



Scheme 1 Methods for synthesis of 3,3,3-trifluoropropanal dialkyl acetals.

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Table 1 Optimization of the reaction conditions<sup>a</sup>

	F <sub>3</sub> C +	CH <sub>3</sub> OH - 2a	Pd/C (1 mol%) additive (2 mol%) O <sub>2</sub> , solvant (20 mL)	F <sub>3</sub> C	o Ja
Entry	Solvent	Co-catalys	t Additive	$T(^{\circ}C)$	$\operatorname{Yield}^{b}(\%)$
1	DMF	CuCl <sub>2</sub>	_	120	Trace
2	PEG400	CuCl <sub>2</sub>	_	120	60
3	Toluene	CuCl <sub>2</sub>	_	120	68
4	THF	$CuCl_2$	_	120	53
5	MeCN	$CuCl_2$	—	120	40
6	MeOH	$CuCl_2$	—	120	92
7	MeOH	CuBr <sub>2</sub>		120	10
8	MeOH	$CuSO_4$		120	0
9	MeOH	—	—	120	0
10	MeOH	$CuCl_2$	LiCl	120	68
11	MeOH	$CuCl_2$	$CH_3SO_3H$	120	80
12	MeOH	$CuCl_2$	$Na_2HPO_4$	120	91
13	MeOH	$CuCl_2$	$K_2CO_3$	120	27
14	MeOH <sup>c</sup>	$CuCl_2$	—	120	48
15	$MeOH^d$	$CuCl_2$	—	120	91
16	MeOH <sup>e</sup>	$CuCl_2$	—	120	Trace
17	MeOH	$CuCl_2$	—	120	0
18	MeOH	$CuCl_2$	—	100	67
19	MeOH	$CuCl_2$	—	80	46
20	MeOH <sup>g</sup>	CuCl <sub>2</sub>	_	120	93

<sup>a</sup> Reaction conditions: 1a (30 mmol), 2a (60 mmol), catalyst (1 mol%), co-catalyst (2 mol%), additive (1 mol%), solvent (20 mL),  $O_2$  1 MPa, 120 °C, 8 h.  $^b$  Yields determined by GC.  $^cO_2$  0.6 MPa.  $^dO_2$  1.4 MPa. <sup>e</sup> O<sub>2</sub> 0 MPa. <sup>f</sup> Catalyst free. <sup>g</sup> PdCl<sub>2</sub> (1 mol%).

Methanol was found to be the optimal solvent providing an excellent yield of 3a. In addition, the effects of co-catalysts such as CuCl<sub>2</sub>, CuBr<sub>2</sub>, and CuSO<sub>4</sub> on yield of reaction were studied (Table 1, entries 6-8). Based on the results, CuCl<sub>2</sub> showed the highest activity among the tested co-catalysts. No target product was observed in the absence of CuCl<sub>2</sub> (Table 1, entry 9). The cocatalyst CuCl<sub>2</sub> could play dual roles, which oxidized Pd<sup>0</sup> to Pd<sup>II</sup> as co-oxidant and also acted as a ligand to prevent the deactivation of the catalyst.18 The influences of additives on catalytic activity were also tested such as LiCl, CH<sub>3</sub>SO<sub>3</sub>H, Na<sub>2</sub>HPO<sub>4</sub> and  $K_2CO_3$  (Table 1, entries 10–13). Although the addition of CH<sub>3</sub>SO<sub>3</sub>H increased the conversion of TFP, the yield of 3,3,3trifluoropropenyl methyl ether (Michael adduct) also increased. However, the use of dibasic Na<sub>2</sub>HPO<sub>4</sub> as an additive could prevent the formation of the Michael adduct, leading to a little decrease of TFP conversion. This result is consistent with Hosokawa's studies.<sup>10a</sup> Finally, the effects of O<sub>2</sub> pressure and temperature were studied. A lower yield of 3a was obtained when the reaction was run at the  $O_2$  pressure of 0.6 MPa (Table 1, entry 14). However, increasing the reaction pressure to 1.4 MPa had no significant effect on the yield of product 3a (Table 1, entry 15). The reaction without  $O_2$  or Pd/C did not give the desired product at all (Table 1, entries 16 and 17). A decrease in the temperature led to a decrease in the yield (Table 1, entries 18 and 19). Furthermore, we compared the catalytic activity of



Fig. 1 Recyclability study of Pd/C catalyst. Reaction conditions: 1a (30 mmol), catalyst (1 mol%), co-catalyst (2 mol%), solvent (20 mL), O2 1 MPa, 120 °C, 8 h. Yields determined by GC.

heterogeneous catalyst Pd/C with homogeneous catalyst PdCl<sub>2</sub>. To our pleasure, the heterogeneous catalyst Pd/C displayed similar activity to the homogeneous catalyst PdCl<sub>2</sub> (Table 1, entry 20). The benefit using heterogeneous catalytic system is that the catalyst is easily separated by filtration. The catalyst recycle was also checked and it was reusable for at least 4 times with the addition of a small amount of  $CuCl_2$  (Fig. 1).

We next explored the scope and the utility of this method with other olefins and various alcohols. Table 2 shows the acetalization of TFP with various alcohols. In almost all the cases tested primary alcohols, the acetalization went smoothly, giving a high yield of the desired products. The substituted groups on the beta position of primary alcohol seemed to have little influence on the product yields (Table 2, entries 3i and 3k). Isopropanol 2l, as secondary alcohol, could also be converted into the corresponding acetal with moderate yield (Table 2, entry 12). However, when cyclohexanol and tert-butyl alcohol were explored, only a little desired product could be detected. In general, the desired products could be obtained with higher yields from primary alcohols than that from secondary alcohols. Additionally, the alcohol containing aromatic ring such as benzyl alcohol leads to the corresponding product of 23% yield, which was also lower than that of primary alcohols because a part of benzyl alcohol was transferred to benzaldehyde and benzyl ether (Table 2, entry 13). Furthermore, the reaction of ethylene glycol with TFP gave the desired product of 32% yield (Table 2, entry 14). Unfortunately, when glycerol was used, the reaction failed to afford the desired product. The reaction of 2aminoethanol also failed to afford the desired product but gave 30 in 73% yield. Those alcohols containing ester, ketone such as methyl glycolate, hydroxyacetone were found to afford a little desired product.

In order to further demonstrate the utility of this protocol, various alkenes were examined. Table 3 shows the acetalization of various olefins with methanol by the Pd/C-CuCl<sub>2</sub> system. Methyl acrylate, ethyl acrylate and *n*-butyl acrylate in methanol provided the corresponding acetals in good yields (Table 3,

 Table 2
 The acetalization of TFP with various alcohols<sup>a</sup>







 $^a$  Reaction conditions: **1a** (30 mmol), **2** (20 mL), Pd/C catalyst (1 mol%), CuCl<sub>2</sub> (2 mol%), O<sub>2</sub> 1 MPa, 120 °C, 8 h.  $^b$  Yields determined by GC. Number in parentheses is isolated yield.

 Table 3
 The acetalization of various olefins with methanol<sup>a</sup>



 $^a$  Reaction conditions: 1 (30 mmol), 2a (20 mL), Pd/C catalyst (1 mol%), CuCl<sub>2</sub> (2 mol%), O<sub>2</sub> 1 MPa, 50 °C, 8 h.  $^b$  Isolated yield.  $^c$  120 °C yields determined by GC.

entries 1–3) which were the useful precursors for the preparation of various heterocyclic compounds.<sup>19</sup> Acrylonitrile afforded the corresponding product in 30% yield (Table 3, entry 4). The decrease in the  $\pi$ -electron density of olefins due to competitive coordination ability of the CN group to Pd<sup>II</sup> retards the reaction.<sup>10a</sup> When styrene was explored, only 10% yield of **4f** was obtained because most of styrene were transferred to hypnone and benzaldehyde (Table 3, entry 5). Unfortunately, when the terminal alkenes bearing substituent on the alpha or beta position such as 2-bromo-3,3,3-trifluoropropene, 2-chloro-3,3,3trifluoropropene, methyl methacrylate and methyl cinnamate were explored, the reaction failed to afford the desired products.

To explore the possible reaction pathway, the Michael adduct 3,3,3-trifluoropropenyl methyl ether **C** was synthesised according to reference.<sup>9</sup> Then the Michael adduct **C** was used to react with methanol under the same conditions of model reaction (Scheme 2). The desired product **D** was obtained in 97% yield.

Based on the previous mechanism reported<sup>10*a*,11*b*</sup> and our results, a plausible pathway is provided in Scheme 3. In this pathway, the key step is the production of the Michael adduct **C**, which has been detected by GC-MS in our experiments. First of all, Pd<sup>0</sup> was oxidized to Pd<sup>II</sup> in the presence of CuCl<sub>2</sub> and O<sub>2</sub> as the conventional redox couples.<sup>11*b*,18*a*</sup> Our experimental results (Table 1, entries 9, 16 and 20) also concludes that the Pd<sup>II</sup> is the true catalytic active species. Second, a Pd<sup>II</sup> catalyst undergoes oxypalladation with **A** to afford a organopalladium intermediate **B**, followed by β-H elimination reaction to intermediate **C**. Finally, the intermediate **C** undergoes oxypalladation again and then affords the desired product **D**. For 2-bromo-3,3,3trifluoropropene, 2-chloro-3,3,3-trifluoropropene and methyl methacrylate, their organopalladium intermediates **B** can not occur β-H elimination reaction because β-H is replaced by Cl, Br



Scheme 2 Synthesis of D from C.



Scheme 3 Possible reaction mechanism.

and CH<sub>3</sub>. So the results that there is no corresponding product for them can be explained.

## Conclusions

In summary, we developed a new strategy for one-step synthesis of 3,3,3-trifluoropropanal dialkyl acetals *via* a simple Pd/C–CuCl<sub>2</sub> system catalyzed acetalization reaction of commercial TFP with alcohols. The catalyst system can be recycled for 4 times without obvious deactivation. The wide scope to a large number of primary alcohols and alkenes with electron-withdrawing substituent, makes this strategy remarkably practical for the synthesis of functional acetal compounds. Atomeconomical characteristics and the recyclable catalyst system of this method are beneficial to industrial applications.

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#### Notes and references

- (a) W. Zhu, J. Wang, S. N. Wang, Z. N. Gu, J. L. Acena, K. Izawa, H. Liu and V. A. Soloshonok, *J. Fluorine Chem.*, 2014, 167, 37; (b) B. J. Deadman, M. D. Hopkin, I. R. Baxendale and S. V. Ley, *Org. Biomol. Chem.*, 2013, 11, 1700; (c) A. K. Chakraborti, S. K. Garg, R. Kumar, H. F. Motiwala and P. S. Jadhavar, *Curr. Med. Chem.*, 2010, 17, 1563; (d) E. L. Luzina and A. V. Popov, *J. Fluorine Chem.*, 2015, 176, 82; (e) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, 114, 2432; (f) C. Marcocci and F. Cetani, *J. Endocrinol. Invest.*, 2012, 35, 90; (g) E. L. Luzina and A. V. Popov, *J. Fluorine Chem.*, 2014, 168, 121.
- 2 B. L. Pilkington, S. Armstrong, N. J. Barnes, S. P. Barnett,
  E. D. Clarke, P. J. Crowley, T. E. M. Fraser, D. J. Hughes,
  C. J. Mathews, R. Salmon, S. C. Smith, R. Viner,
  W. G. Whittingham, J. Williams, A. J. Whittle,
  W. R. Mound and C. J. Urch, WO Patent 2001055144, 2001.
- 3 (a) A. Thompson, E. G. Corely, M. F. Huntington, E. J. J. Grabowski, J. F. Remenar and D. B. Collum, J. Am. Chem. Soc., 1998, 120, 2028; (b) L. Tan, C. Y. Chen, R. D. Tillyer, E. J. J. Grabowski and P. J. Reider, Angew. Chem., Int. Ed., 1999, 38, 711; (c) J. Walkowiak-Kulikowska, A. Szwajca, F. Boschet, V. Gouverneur and B. Ameduri, Macromolecules, 2014, 47, 8634; (d) T. Kobayashi, T. Eda, O. Tamura and H. Ishibashi, J. Org. Chem., 2002, 67, 3156; (e) T. Chiba, R. Hung, S. Yamada, B. Trinque, M. Yamachika, C. Brodsky, K. Pattersion, A. Vander Heyden, A. Jamison, S. H. Lin, M. Somervell, J. Byers, W. Conley and C. G. Willson, J. Photopolym. Sci. Technol., 2000, 13, 657.

- 4 (a) V. P. Kukhar, A. E. Sorochinsky and V. A. Soloshonok, *Future Med. Chem.*, 2009, 1, 793; (b) A. E. Sorochinsky and V. A. Soloshonok, J. Fluorine Chem., 2010, 131, 127; (c) J. L. Acena, A. Simon Fuentes and S. Fustero, Curr. Org. Chem., 2010, 14, 928; (d) J. L. Acena, A. E. Sorochinsky and V. A. Soloshonok, Synthesis, 2012, 44, 1591; (e) K. V. Turcheniuk, V. P. Kukhar, G. V. Roschenthaler, J. L. Acena, V. A. Soloshonok and A. E. Sorochinsky, RSC Adv., 2013, 3, 6693; (f) J. L. Acena, A. E. Sorochinsky, H. Moriwaki, T. Sato and V. A. Soloshonok, J. Fluorine Chem., 2013, 155, 21.
- 5 (a) M. A. McClinton and D. A. McClinton, *Tetrahedron*, 1992,
  48, 6555; (b) J.-P. Begue and D. Bonnet-Delpon, *Tetrahedron*, 1991, 47, 3207.
- 6 (a) G. Q. Shi and Y. Xu, J. Chem. Soc., Chem. Commun., 1989, 609; (b) B. Jiang and Y. Xu, J. Org. Chem., 1991, 56, 7336; (c) I. Ojim, Chem. Rev., 1988, 88, 1011; (d) F. Hong, X. Tang and C. Hu, J. Chem. Soc., Chem. Commun., 1994, 289; (e) K. Mizutani, T. Yamazaki and T. Kitazume, J. Chem. Soc., Chem. Commun., 1995, 51; (f) G. Q. Shi, X. H. Huang and F. Hong, J. Org. Chem., 1996, 61, 3200; (g) G. Q. Shi, X. H. Huang and F. Hong, J. Chem. Soc., Perkin Trans. 1, 1996, 1, 763.
- 7 T. Komata, S. Akiba, K. Hosoi and K. Ogura, *J. Fluorine Chem.*, 2008, **129**, 35.
- 8 (a) F. Hong and C. M. Hu, J. Chem. Soc., Perkin Trans. 1, 1997,
  1, 1909; (b) M. E. Gihani and H. Heaney, Synlett, 1993, 583; (c)
  T. Mukaiyama and M. Hayashi, Chem. Lett., 1974, 15; (d)
  A. Ghribi, A. Alexakis and J. F. Normant, Tetrahedron Lett., 1984, 25, 3075.
- 9 F. Hong and C. M. Hu, Chem. Commun., 1996, 57.
- 10 (a) T. Hosokawa, T. Ohta, S. Kanayama and S. Murahashi, J. Org. Chem., 1987, 52, 1758; (b) T. Hosokawa, Y. Ataka and S. Murahashi, Bull. Chem. Soc. Jpn., 1990, 63, 166; (c) T. Hosokawa, S. Aoki and S. Murahashi, Synthesis, 1992, 11, 558; (d) T. Hosokawa and S. Murahashi, Acc. Chem.

Res., 1990, 23, 49; (e) T. Hosokawa, T. Yamanaka, M. Itotani and S. Murahashi, J. Org. Chem., 1995, 60, 6159.

- 11 (a) H. F. Jiang, Y. X. Shen and Z. Y. Wang, *Tetrahedron*, 2008,
  64, 508; (b) Z. Y. Wang, H. F. Jiang, X. Y. Quyang, C. R. Qi and
  S. R. Yang, *Tetrahedron*, 2006, 62, 9846; (c) Z. Y. Wang,
  H. F. Jiang, C. R. Qi, Y. G. Wang, Y. S. Dong and H. L. Liu, *Green Chem.*, 2005, 7, 582.
- 12 A. Kishi, S. Sakaguchi and Y. Ishii, Org. Lett., 2000, 2, 523.
- 13 J. H. Zhou, Z. P. Dong, H. L. Yang, Z. Q. Shi, X. C. Zhou and R. Li, *Appl. Surf. Sci.*, 2013, **279**, 360.
- 14 (a) L. H. Albert and K. Samuel, J. Am. Chem. Soc., 1950, 72, 3369; (b) L. H. Albert and N. Maxwell, J. Am. Chem. Soc., 1951, 73, 5527; (c) L. Kin and L. Sean, Appl. Phys. Lett., 2001, 79, 4225; (d) J. R. Li, J. R. Xu and M. Q. Zhang, Carbon, 2003, 41, 2353; (e) E. B. Donald, W. N. Mae and J. W. James, J. Chem. Soc., Perkin Trans. 1, 1983, 1, 741; (f) Y. Bai, J. J. Peng and Y. Q. Hu, J. Fluorine Chem., 2011, 132, 123.
- 15 (a) S. X. Hang, A. H. Xu and B. Geng, *J. Appl. Polym. Sci.*, 2007, 105, 533; (b) K. George, A. Bruno and M. B. Stephan, *J. Fluorine Chem.*, 2007, 128, 910.
- 16 (a) T. Fuchikami and I. Ojima, J. Am. Chem. Soc., 1982, 104, 3527; (b) O. Iwao, K. Koji and O. Masami, J. Am. Chem. Soc., 1987, 109, 7714; (c) F. Shibahara, K. Nozaki and T. Hiyama, J. Am. Chem. Soc., 2003, 125, 8560; (d) F. Takamasa, O. Katsuyuki and O. Iwao, J. Org. Chem., 1983, 48, 3807.
- 17 (a) P. V. Ramachandran and M. P. Jennings, *Chem. Commun.*, 2002, 386; (b) P. V. Ramachandran, M. P. Jennings and C. B. Herbert, *Org. Lett.*, 1999, 1, 1402.
- 18 (a) J. A. Keith, R. J. Nielsen, J. Oxgaard and W. A. Goddard, J. Am. Chem. Soc., 2007, 129, 12342; (b) K. Fagnou and M. Lautens, Angew. Chem., Int. Ed., 2002, 41, 26.
- 19 (a) J. Tsuji, Synthesis, 1990, 9, 739; (b) J. P. Collman,
  A. O. Chong, G. B. Jameson, R. T. Oakley, E. Rose,
  E. R. Schmittou and J. A. Ibers, J. Am. Chem. Soc., 1981, 103, 516.