Copper(I) hexafluorophosphate: a dual functional catalyst for three-component reactions of methyl phenyldiazoacetate with alcohols and aldehydes or α-ketoesters

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ARTICLE INFO

ABSTRACT

Oxonium ylides in situ generated from methyl phenyldiazoacetate and alcohols in the presence of $CuPF_6(CH_3CN)_4$ underwent an aldol-type reaction with aldehydes or α-ketoesters in a convergent, three-component fashion to give α-alkoxyl-β-hydroxyl acid derivatives in good yields.

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The chemistry of onium ylides is an area of continuing interest. Carbonyl,[1] phosphorus,[2] sulfur,[3] ammonium,[4] and oxonium[5] ylides have been widely utilized in organic synthesis. In the study of oxonium ylides derived from metal carbenoids, the [2,3]-sigmatropic[6] and [1,2]-stevens[7] rearrangements have been shown to be powerful strategies for synthesis of hetero-atom-containing compounds. We have discovered a new chemistry of oxonium ylides that alcoholic oxonium ylides generated in situ from a diazocompound and an alcohol catalyzed by $Rh_2(OAc)_4$ can be trapped by aldehydes and imines through an aldol-type nucleophilic addition.[8] A proposed reaction pathway is shown in Scheme 1. Due to competing intramolecular 1,2-H shift reaction of the ylide intermediates Ia/

Ib, the dirhodium-catalyzed reaction was limited to electron-deficient aromatic aldehydes in the absence of other additives.[9]

Copper is a versatile, abundant, and cheap catalyst in organic synthesis.[1b] Cu complexes show many differences in cyclopropanation, aziridination, O–H insertion, N–H insertion, etc. versus rhodium-catalyzed diazo decomposition reactions.[10] In the alcoholic oxonium ylide trapping process, a copper catalyst may play a dual role. On the one hand, it serves as a catalyst for the diazo decomposition to generate the alcoholic oxonium ylide in situ. On the other hand, it may function as a Lewis acid to activate trapping reagents such as aldehydes to be more reactive electrophiles. We envision that, by employing an appropriate copper catalyst, the current reaction scope could be greatly extended. In this Letter, we report that $CuPF_6(CH_3CN)_4$ is an excellent catalyst for the three-component aldol-type reaction. With the use of the copper catalyst, the reaction is not only good for various aldehydes, but it also extends the available electrophilic substrates to include α-ketoesters to give good yields of α-alkoxyl-β-hydroxyl acid derivatives bearing two vicinal tetrasubstituted carbon centers. Such compounds are highly important intermediates in the synthesis of a variety of medicinal agents and natural products.[11]

To validate our hypothesis regarding the potential of copper catalysts in the three-component reactions of methyl aryl diazoacetates, alcohols, and aldehydes, a number of Cu complexes were screened in the reaction. While $Cu(OTf)_2$, CuOTf, $Cu(acac)_2$, and $Cu(pfacac)_2$ gave only the O-H insertion product with benzaldehyde (**3a**), we were glad to find that the use of $CuPF_6(CH_3CN)_4$[12] gave a 74% yield of the desired three-component reaction product **4a**. In contrast, the use of the $Rh_2(OAc)_4$ catalyst gave only a 6% yield of the desired product (Table 1, entry 1). A series of aldehydes have been investigated using $CuPF_6(CH_3CN)_4$ (Table 1).[13] Both aromatic and aliphatic aldehydes[9] gave the desired products with reasonable yields (Table 1, entries 10 and 11). To the best of our
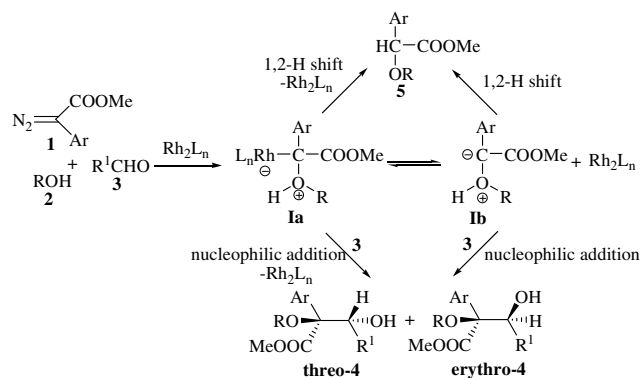
Scheme 1. A proposed reaction pathway for trapping alcoholic oxonium ylides with aldehydes.

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Table 1
CuPF$_6$(CH$_3$CN)$_4$-catalyzed three-component reactions of methyl phenyldiazoacetate (**1**) with benzyl alcohol (**2a**) and aldehydes (**3**)[a]
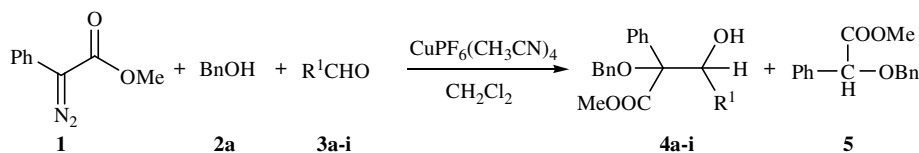
Entry	R^1	Yield of **4**[b] (%)	**4:5**[c]	Isomer ratio of **4** threo:erythro[c]
1[d]	Ph(**3a**)	6(**4a**)	10:90	—[e]
2[g]	Ph(**3a**)	—[f]	0:100	—[f]
3	Ph(**3a**)	74(**4a**)	79:21	81:19
4	p-NO$_2$Ph(**3b**)	83(**4b**)	89:11	74:26
5	o-NO$_2$Ph(**3c**)	78(**4c**)	92:8	69:31
6	2,4-NO$_2$Ph(**3d**)	85(**4d**)	93:7	27:73
7	p-CF$_3$Ph(**3e**)	75(**4e**)	92:8	83:17
8	p-CN Ph(**3f**)	62(**4f**)	83:17	83:17
9	p-MeOPh(**3g**)	50(**4g**)	56:44	72:28
10	Et(**3h**)	48(**4h**)	53:47	83:17
11	^{n}Pr(**3i**)	38(**4i**)	41:59	81:19

[a] All the reactions were carried out in refluxing CH$_2$Cl$_2$ for 2 h with **1:2:3** = 1.0:1.2:1.2 (mmol) by using 10 mol % CuPF$_6$(CH$_3$CN)$_4$.
[b] Isolated yields after column chromatography purification.
[c] Determined by ^{1}H NMR of the unpurified reaction mixtures.
[d] Using 1 mol % Rh$_2$(OAc)$_4$ in stead of CuPF$_6$(CH$_3$CN)$_4$.
[e] Not determined.
[f] Not detected.
[g] The reaction was carried out with 10 mol % CuOTf catalyst.

knowledge, this is the first such demonstration for aliphatic aldehydes.

With the CuPF$_6$(CH$_3$CN)$_4$ catalyst, the substrates were extended to α-ketoesters. While Rh$_2$(OAc)$_4$ gave no desired three-component reaction product with methyl phenyl α-ketoester **6a** (Table 2, entry 1), copper(I) hexafluorophosphate generated the anticipated α-hydroxyl-β-alkoxy acid derivatives bearing two tetrasubstituted carbon centers in 68% yield (Table 2, entry 2). The results for methyl phenyldiazoacetate with a number of alcohols and α-ketoesters are summarized in Table 2 (entries 3–14). The resulting α-hydroxyl-β-alkoxy ester derivatives are not readily synthesized using traditional methods. The structure and relative configuration of isomer **7a** was confirmed by single-crystal X-ray[14] (Fig. 1) anal-

ysis to be threo. Extending the method with the CuPF$_6$(CH$_3$CN)$_4$ catalyst to other electrophiles, such as ketones and α,β-unsaturated ketones, did give the desired products but with much lower yield (<30%).

The proposed reaction mechanism for the Cu-catalyzed three-component reaction is shown in Scheme 2.[1b,10d,12] CuPF$_6$(CH$_3$CN)$_4$ not only catalyzes diazo decomposition in the presence of an alcohol to form an alcoholic oxonium ylide but also serves as a Lewis acid to activate the aldehydes or α-ketoesters.

In conclusion, we have found that CuPF$_6$(CH$_3$CN)$_4$ is an effective catalyst in the three-component reaction of methyl phenyldiazoacetate with alcohols and aldehydes or α-ketoesters. CuPF$_6$-(CH$_3$CN)$_4$ plays a dual role in the reaction, the scope of which

Table 2
CuPF$_6$(CH$_3$CN)$_4$-catalyzed three-component reactions of methyl phenyldiazoacetate (**1**) with alcohols (**2**) and α-ketoesters (**6**)[a]
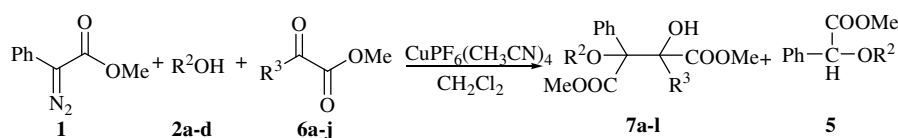
Entry	R^2	R^3	Yield of **7**[b] (%)	**7:5**[c]	threo-**7**:erythro-**7**[c]
1[d]	Bn(**2a**)	Ph(**6a**)	—[e]	0:100	—
2	Bn(**2a**)	Ph(**6a**)	68(**7a**)	85:15	41:59
3	Me(**2b**)	Ph(**6a**)	69(**7b**)	84:16	50:50
4	Et(**2c**)	Ph(**6a**)	72(**7c**)	88:12	43:57
5	^{i}Pr(**2d**)	Ph(**6a**)	—	0:100	—
6	Bn(**2a**)	p-ClPh(**6b**)	75(**7d**)	94:6	50:50
7	Bn(**2a**)	m-ClPh(**6c**)	72(**7e**)	90:10	41:59
8	Bn(**2a**)	o-ClPh(**6d**)	40(**7f**)	48:52	41:59
9	Bn(**2a**)	p-BrPh(**6e**)	75(**7g**)	93:7	49:51
10	Bn(**2a**)	p-FPh(**6f**)	71(**7h**)	90:10	49:51
11	Bn(**2a**)	p-NO$_2$Ph(**6g**)	76(**7i**)	95:5	47:53
12	Bn(**2a**)	p-MeOPh(**6h**)	65(**7j**)	72:28	50:50
13	Bn(**2a**)	(E)-styryl(**6i**)	60(**7k**)	95:5	48:52
14	Bn(**2a**)	Me(**6j**)	80(**7l**)	92:8	22:78

[a] All the reactions were carried out in refluxing CH$_2$Cl$_2$ for 2h with **1:2:6** = 1.0:1.2:1.2 (mmol) by using 10 mol % CuPF$_6$(CH$_3$CN)$_4$.
[b] Isolated yields after chromatography purification.
[c] Determined by ^{1}H NMR of the unpurified reaction mixtures.
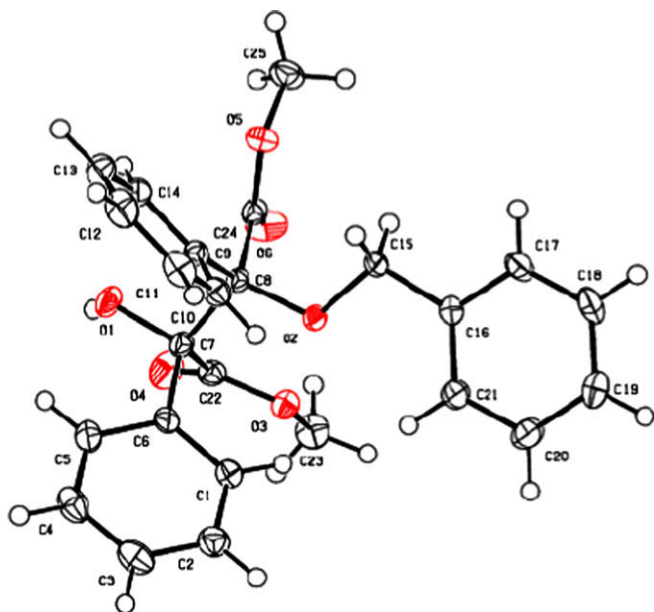[d] Using 1 mol % Rh$_2$(OAc)$_4$ in stead of CuPF$_6$(CH$_3$CN)$_4$.
[e] Not detected.

Figure 1. X-ray structure of *threo*-**7a**.

was extended to aliphatic aldehydes and α-ketoesters. We expect that employing appropriate chiral ligands would allow asymmetric catalysis in the current three-component reaction, and are currently pursuing such research in our laboratory.

Acknowledgements

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.090.

References and notes

1. (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223; (b) Doyle, M. P.; Mckervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley and Sons: New York, 1998; (c) Lu, C. D.; Chen, Z. Y.; Liu, H.; Hu, W. H.; Mi, A. Q.; Doyle, M. P. *J. Org. Chem.* **2004**, *69*, 4856.
2. (a) Maryanoff, B. E.; Retiz, A. B. *Chem. Rev.* **1989**, *89*, 863; (b) Aggarwal, V. K.; Fulton, J. R.; Sheldon, C. G.; Vicente, J. D. *J. Am. Chem. Soc.* **2003**, *125*, 6034.
3. (a) Mori, T.; Sawada, Y.; Oku, A. *J. Org. Chem.* **2000**, *65*, 3620; (b) Reddy, L. R.; Gais, H. J.; Woo, C. W.; Raabe, G. *J. Am. Chem. Soc.* **2002**, *124*, 10427; (c) Aggarwal, V. K.; Richardson, J. *Chem. Commun.* **2003**, 2644; (d) Aggarwal, V. K.; Vasse, J. L. *Org. Lett.* **2003**, *5*, 3987.
4. (a) Doyle, M. P.; Tamblvn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094; (b) Vanecko, J. A.; West, F. G. *Org. Lett.* **2002**, *4*, 2813.
5. (a) Pirrung, M. P.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060; (b) Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817; (c) West, F. G.; Eberlein, T. H.; Tester, R. W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2857; (d) Tester, R. W.; West, F. G. *Tetrahedron Lett.* **1998**, *39*, 4631.
6. (a) Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193; (b) Clark, J. S.; Dossetter, A. G.; Blake, A. J.; Whittingham, W. S.; Li, W. G. *Chem. Commun.* **1999**, 749; (c) Clark, J. S.; Bate, A. L.; Grinter, T. *Chem. Commun.* **2001**, 459; (d) Clark, J. S.; Whitlock, G.; Jiang, S.; Onyia, N. *Chem. Commun.* **2003**, 2578; (f) Clark, J. S.; Fessard, T. S.; Wilson, C. *Org. Lett.* **2004**, *6*, 1773.
7. (a) Eberlein, T. H.; West, F. G.; Tester, R. W. *J. Org. Chem.* **1992**, *57*, 3479; (b) West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892; (c) Marmsater, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144; (d) Marmsater, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron* **2002**, *58*, 2027; (e) Marmsater, F. P.; Murphy, G. K.; West, F. G. *J. Am. Chem. Soc.* **2003**, *125*, 14724.
8. (a) Lu, C. D.; liu, H.; Chen, Z. Y.; Hu, W. H.; Mi, A. Q. *Org. Lett.* **2005**, *7*, 83; (b) Huang, H. X.; Guo, X.; Hu, W. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1337; (c) Hu, W. H.; Xu, X. F.; Zhou, J.; Liu, W. J.; Hu, J.; Yang, L. P.; Gong, L. Z. *J. Am. Chem. Soc*, **2008**, ASAP.
9. Lu, C. D.; liu, H.; Chen, Z. Y.; Hu, W. H.; Mi, A. Q. *Chem. Commun.* **2005**, 2624.
10. (a) Evans, D. A.; woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726; (b) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676; (c) Pqrez, P. J.; Brookhart, M.; Templeton, J. L. *Organometallics* **1993**, *12*, 261; (d) Kirmse, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 1088; (e) Doyle, M. P.; Yan, M.; Hu, W. H. *J. Am. Chem. Soc.* **2003**, *125*, 4692; (f) Thomas, C. M.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 4594; (g) Yue, Y. L.; Wang, Y. H.; Hu, W. H. *Tetrahedron Lett.* **2007**, *48*, 3975.
11. (a) Seebach, D. In *Modern Synthetic Method*; Scheffold, R., Ed.; Otto Salle: Frankfurt, 1980; (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071; (c) Shibasaki, M.; Nishikimi, Y.; Iimori, T.; Sodeoka, M. *J. Org. Chem.* **1989**, *108*, 3354; (d) Evans, D. A.; Kozlowski, M. C.; Burgey, S. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1998**, *119*, 7893; (e) Grover, P. T.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. *J. Org. Chem.* **2000**, *65*, 6283.
12. (a) Kubas, G. J. *Inorg. Synth.* **1979**, *19*, 90; (b) Doyle, M. P.; Peterson, C. S.; Parker, D. L. *Angew. Chem., Int. Ed.* **1996**, *35*, 1334; (c) Doyle, M. P.; Peterson, C. S.; Protopopova, M. N.; Marnett, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 8826; (d) Doyle, M. P.; Peterson, C. S.; Zhou, Q. L.; Nishiyama, H. *Chem, Commun.* **1997**, *2*, 211; (e) Doyle, M. P.; Chapman, B. J.; Hu, W. H. *Org. Lett.* **1999**, *1*, 1327; (f) Doyle, M.
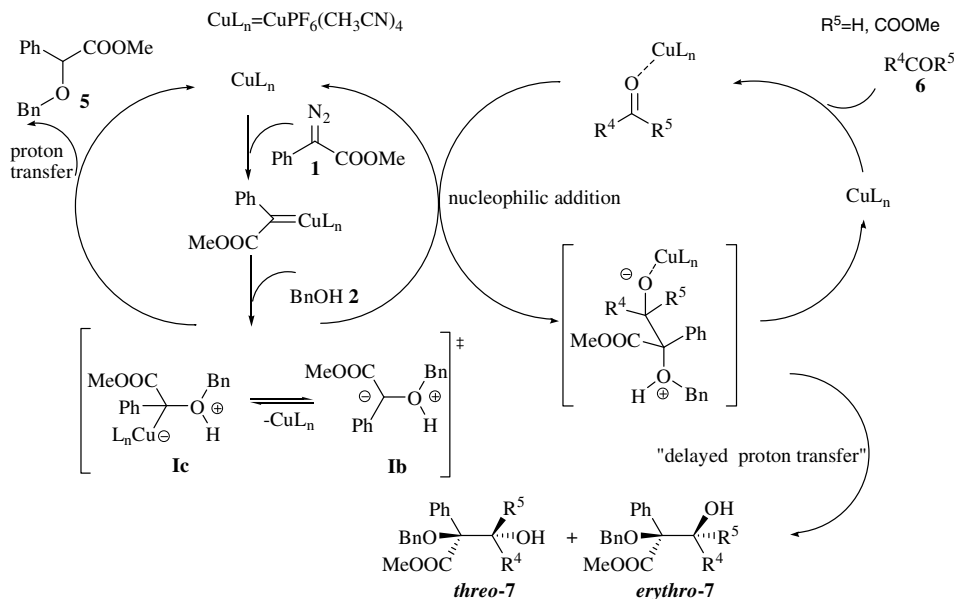
Scheme 2. Proposed reaction mechanism for CuPF$_6$(CH$_3$CN)$_4$ catalyzed three-component reactions of methyl phenyldiazoacetate with benzyl alcohol and aldehydes or α-ketoesters.

P.; Hu, W. H. *J. Org. Chem.* **2000**, *65*, 8839; (g) Doyle, M. P.; Hu, W. H.; Chapman, B.; Marnett, A. B. *J. Am. Chem. Soc.* **2000**, *122*, 5718.

13. *General procedure*: To a CH_2Cl_2 solution of $CuPF_6(CH_3CN)_4$ (0.10 mmol), aldehydes (1.2 mmol), and alcohols (1.2 mmol) was added methyl phenyldiazoacetate (1.0 mmol) in CH_2Cl_2 via a syringe pump over 1 h under refluxing. After completing the addition, the reaction mixture was cooled to room temperature. Solvent was removed, and $CuPF_6$ was removed from the residue by flash column chromatography on silica gel by using EtOAc as an eluent. A portion of the resulting crude product was subjected to ^{1}H NMR analysis for the determination of product ratio and diastereoselectivities. The crude product was further purified by column chromatography on silica gel using EtOAc–light petroleum as eluents to give desired products.

14. CCDC 686084, Crystal data for *threo*-7a: $C_{25}H_{24}O_6$, M_w = 420.44, monoclinic, space group $P2(1)/c$, a = 13.0138(3) Å, b = 8.7546(2) Å, c = 18.6199(3) Å, β = 100.958(1), V = 2082.70(8) Å^3, Z = 4, ρ_{catcd} = 1.341 Mg/m^3, $F(0\,0\,0)$ = 888, λ = 0.71073 Å, T = 153(2) K, μ(Mo-Kα) = 0.096 mm^{-1}. Data for the structure were collected on a Siemens P-4X four-circle diffractometer. Intensity measurements were performed on a crystal (dimensions 0.54 × 0.50 × 0.38 mm). In the range 6.28 < 2θ < 54.96, of the 4766 measured reflections, 4336 were independent (R_{int} = 0.014). The structures were solved by direct methods (SHELXS-97) and refined by full-matrix least-squares on F^2. The final refinements converged at R_1 = 0.0352 for $I > 2\sigma(I)$ and wR_2 = 0.0983 for all data. The final difference Fourier synthesis gave a min/max residual electron density of −0.225/+0.358 e Å^{-3}.