

A Cyanide-Free Synthesis of Acylcyanides through Ru-Catalyzed C(sp³)-H-Oxidation of Benzylic Nitriles

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A practical method for generation of acylcyanides devoid of any external cyanide sources is presented that relies on a mild Ru-catalyzed selective C–H-oxidation of benzylic nitriles. The starting materials are smoothly generated through condensation of the corresponding carboxylic acid amides using silanes. The obtained acylcyanides can be employed in a plethora of transformation as exemplified to some larger extend in the sequence of C–H-oxidation-Tischenko-rearrangement for the generation of structurally diverse benzoyloxycyanohydrines.

Acylcyanides are versatile building blocks in Organic synthesis.^[1] They can be used as both acylating reagents but also in cross-couplings^[2] and addition reactions^[3] but also in carbonylcyanation of alkynes^[4] or the formation of cyanohydrins (Figure 1).^[5]

At the outset of our studies 4-methoxyphenylacetonitrile and the conditions for the previously reported benzylic C–H oxidation were chosen for the initial experiments and further optimized. We were delighted to find that after a slight modification of the previously established reactions conditions the corresponding acylcyanide **2** was obtained in 97% yield. As expected, electron-rich acetonitriles give higher yields but moderately electron withdrawing groups like halides are tolerated as well. Interestingly, even acetals are stable under the conditions, neither hydrolysis nor oxidation to the corresponding carbonates were observed. As acylcyanides are highly reactive,^[1] the crude acylcyanides were trapped as *t*-butylesters by simple treatment with *t*-butanol in the presence of base (Table 1).

As pointed out above, acylcyanides are highly reactive intermediates which are difficult to isolate. In the fate of practicability we subsequently wondered, whether the reaction mixture could be quenched through the addition of nucleophiles.^[11] While in the case of *t*-butanol a switch of solvents proved necessary, both secondary and primary alcohols could be added directly after full conversion in the

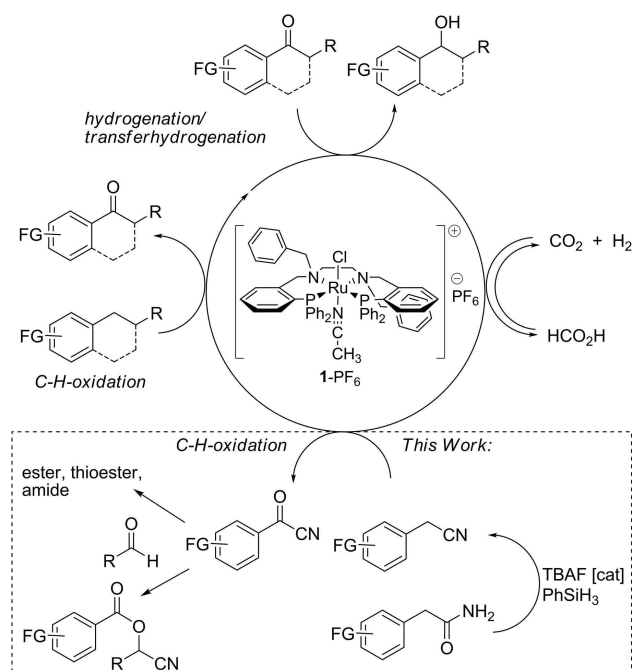


Figure 1. Ru-catalyzed selective C–H-oxidation of benzylnitriles.

Table 1. Ru-catalyzed oxidation of benzylnitriles and in-situ trapping.

[a] All reactions were performed on a 0.5 mmol scale under a nitrogen atmosphere.

[b] Yields of acyl cyanides were determined by ¹H NMR in CDCl₃ using mesitylene as an internal standard

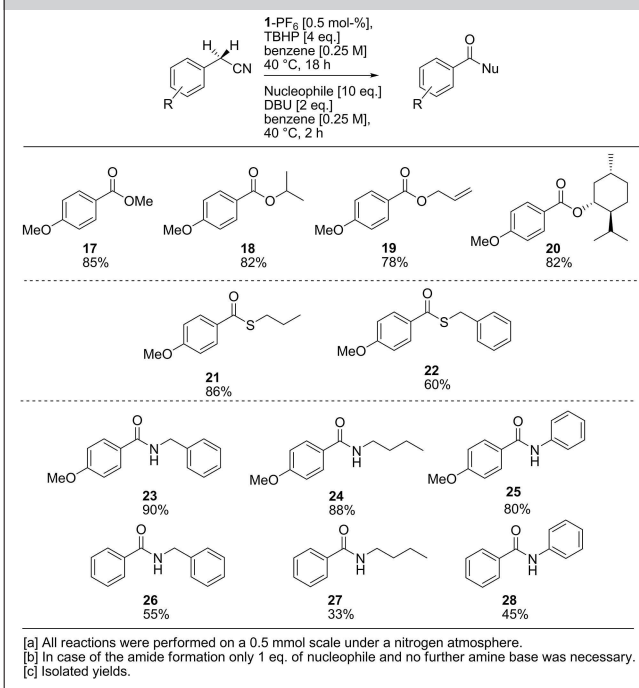
[c] Yields of esters are isolated yields.

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Table 2. Sequential C–H oxidation-nucleophilic substitution.



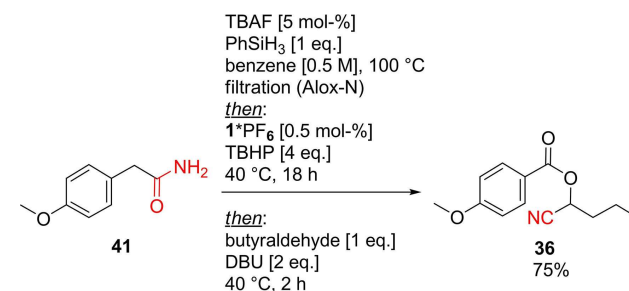
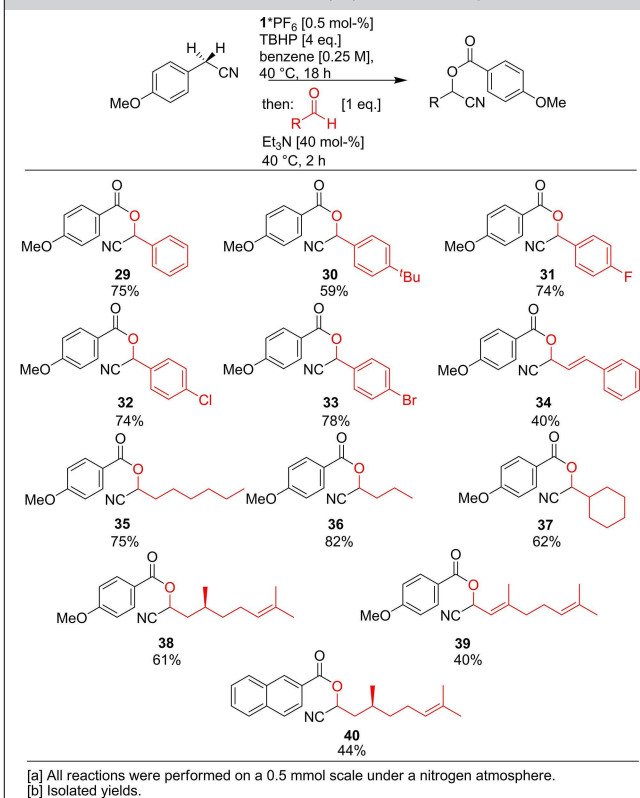
catalytic C–H-oxidation to obtain the corresponding esters in good to excellent yields (Table 2). Moreover, thiols but also amines can be employed. Deterious side reaction due to remaining catalyst and/or oxidant were not observed.

Apart from the use of acylcyanides as acylating agents, their transformation into acylcyanohydrins through base-mediated reaction with aldehydes is an important application (Table 3).

Knowing that the in-situ trapping experiments provide access to different ester, thioesters, and amides (Table 2), we became interested in tying up both processes. Indeed, upon addition of 0.4 equiv. of triethylamine and 1 equiv. of aldehyde to the in-situ formed acylcyanide delivered the corresponding cyanohydrins in good to excellent yields (Table 3). Both aromatic and aliphatic aldehydes were tolerated and converted in good yields. α,β -unsaturated aldehydes like Cinnamaldehyde (Table 3, compound 34) or Citral (Table 3; compounds 39) were converted without observation of the 1,4-addition product. In case of (S)-(–)-citronellal retention of the stereocenter and a single diastereomer was observed (Table 3, compound 38).

A variety of methods for the synthesis of nitriles has been reported in the literature.^[12] Apart from the classical preparation via nucleophilic substitution using cyanide salts,^[13] the dehydration of carboxylic acid amides is the most prominent synthetic approach.^[14] Classical methods for the dehydration rely on the use of dehydrating agents like P₂O₅, PCl₅, etc. under high temperature.^[15] Most recently, catalytic versions for amide dehydration to nitriles were described.^[16] To showcase the synthetic utility of the oxidative preparation of acylcyanides, we coupled both processes (Scheme 1). The fluoride-catalyzed dehydration delivered after filtration over Alox-N (removal of silicon by-products) a solution of the nitrile which was directly

Table 3. Sequential C–H oxidation-acylcyanide rearrangement.



Scheme 1. Cyanide-free synthesis of acylcyanohydrinesters starting from carboxylic acid amides.

oxidized and after addition of butyraldehyde and amine base transferred into the benzoylcyanohydrine in about 75% yield.

In summary we were able to develop a convenient cyanide salt free method for the preparation of benzoyl cyanides which are versatile and reactive compounds. Conversion of those benzoyl cyanides into the valuable cyanohydrin esters is possible under these conditions in a one-pot sequence.

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Conflict of interest

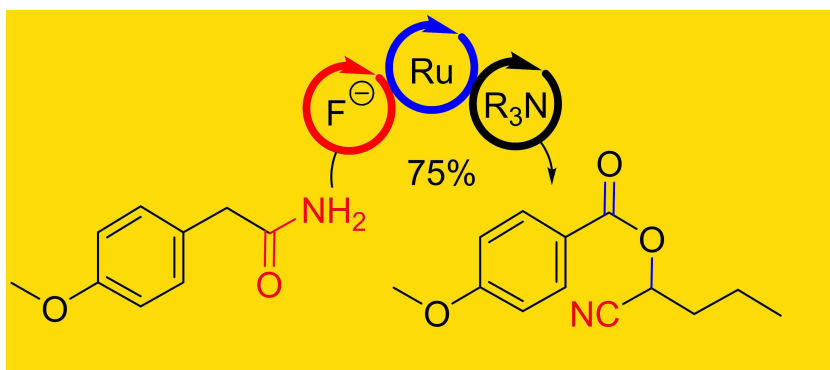
The authors declare no conflict of interest.

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- [1] a) S. Hunig, R. Schaller, *Angew. Chem. Int. Ed.* **1982**, *21*, 36–49; *Angew. Chem.* **1982**, *94*, 1–15; b) J. Thiesing, D. Witzel, A. Brehm, *Angew. Chem.* **1956**, *68*, 425–435.
- [2] C. Duplais, F. Bures, I. Sapountzis, T. J. Korn, G. Cahiez, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 2968–2870; *Angew. Chem.* **2004**, *116*, 3028–3030.
- [3] S. Lundgren, E. Wingstrand, C. Moberg, *Adv. Synth. Catal.* **2007**, *349*, 364–372.
- [4] a) X. Zhang, X. Xie, Y. Liu, *J. Am. Chem. Soc.* **2018**, *140*, 7385–7389; b) S. Arai, T. Sato, Y. Koike, M. Hayashi, A. Nishida, *Angew. Chem. Int. Ed.* **2009**, *48*, 4528–4531; *Angew. Chem.* **2009**, *121*, 4598–4601.
- [5] For a review on this topic see: R. J. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649–3682.
- [6] a) N. Biber, K. Möws, B. Plietker, *Nat. Chem.* **2011**, *3*, 938–942; b) K. Lindermayr, B. Plietker, *Angew. Chem. Int. Ed.* **2013**, *52*, 12183–12186; *Angew. Chem.* **2013**, *125*, 12405–12408; c) F. Horeischi, N. Biber, B. Plietker, *J. Am. Chem. Soc.* **2014**, *136*, 4026–4030; d) F. Horeischi, C. Guttroff, B. Plietker, *Chem. Commun.* **2015**, *51*, 2259–2261; e) C. Socolsky, B. Plietker, *Chem. Eur. J.* **2015**, *21*, 3053–3061; f) C. Guttroff, A. Baykal, H. Wang, P. Popella, F. Kraus, N. Biber, S. Krauss, F. Götz, B. Plietker, *Angew. Chem. Int. Ed.* **2017**, *56*, 15852–15856; *Angew. Chem.* **2017**, *129*, 16065–16070; g) For a review on the natural product class of PPAP see: R. Ciochina, R. Grossman, *Chem. Rev.* **2006**, *106*, 3963–3986.
- [7] S.-F. Hsu, B. Plietker, *ChemCatChem* **2013**, *5*, 126–129.
- [8] S.-F. Hsu, B. Plietker, *Chem. Eur. J.* **2014**, *20*, 4242–4245.
- [9] S.-F. Hsu, S. Rommel, P. Eversfield, K. Muller, E. Klemm, W. R. Thiel, B. Plietker, *Angew. Chem. Int. Ed.* **2014**, *53*, 7074–7078; *Angew. Chem.* **2014**, *126*, 7194–7198.
- [10] a) For a Ru-catalyzed oxidation of nitriles see: S. I. Murahashi, T. Naota, T. Kuwabara, *Synlett* **1989**, 62–63; b) For a Ru-catalyzed synthesis of acylcyanides through dehydrogenation of cyanohydrines see: K. Kim, A. M. P. Moeljadi, H. H. S. H. Hong, *Adv. Synth. Catal.* **2017**, *359*, 3292–3298; c) For a catalytic photooxidation see: Y. Sugiura, Y. Tachikawa, Y. Nagasawa, N. Tada, A. Itoh, *RSC Adv.* **2015**, *5*, 70883–70886.
- [11] a) For amide formation see: X. Chen, T. Chen, Q. Li, Y. Zhou, L.-B. Han, S.-F. Yin, *Chem. Eur. J.* **2014**, *20*, 12234–12238; b) L.-Y. Zhang, C. Zhang, T. Wang, Y.-L. Shi, M.-T. Ban, D.-M. Cui, *J. Org. Chem.* **2019**, *84*, 536–543; c) For ester formation see: W. Kong, B. Li, X. Xu, Q. Song, *J. Org. Chem.* **2016**, *81*, 8436–8443.
- [12] a) D. Mowry, *Chem. Rev.* **1948**, *42*, 189–283; b) G. Yan, Y. Zhang, J. Wang, *Adv. Synth. Catal.* **2017**, *359*, 4068–4105.
- [13] a) G. Hausknecht, *Ber. Dtsch. Chem. Ges.* **1889**, *22*, 324–330; b) W. Tschelinzeff, W. Schmidt, *Ber. Dtsch. Chem. Ges. A/B* **1929**, *62*, 2210–2214; c) M. Tanaka, *Tetrahedron Lett.* **1980**, *21*, 2959–2962; d) T. Ando, T. Kawate, J. Yamawaki, T. Hanafusa, *Synthesis* **1983**, 637–638; e) Y. Cao, Y. Du, B. Chen, J. Li, *Synth. Commun.* **2004**, *34*, 2951–2957.
- [14] For review see: N. K. Bhattacharyya, S. Jha, S. Jha, T. Bhutia, G. Adhikary, *Intern. J. Chem. Appl.* **2012**, *4*, 295–304.
- [15] D. Reisner, E. Hornig, *Org. Synth.* **1950**, *30*, 22.
- [16] S. Zhou, K. Junge, D. Addis, S. Das, M. Beller, *Org. Lett.* **2009**, *11*, 2461–2464.

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COMMUNICATIONS



Three on one strike: The Ru-catalyzed C–H-oxidation of benzylnitrile derivatives provides access toward reactive acylcyanides which can be transformed in-situ into esters, amides, but also into acylcyanohydrines. Upon

coupling the process to a fluoride-catalyzed dehydrogenation of carboxylic acid amides allows for a three-step, one-pot preparation of acylcyanohydrines without the need to employ cyanide salts.

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