Biocatalysis Hot Paper

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Biocatalytic Friedel–Crafts Acylation and Fries Reaction

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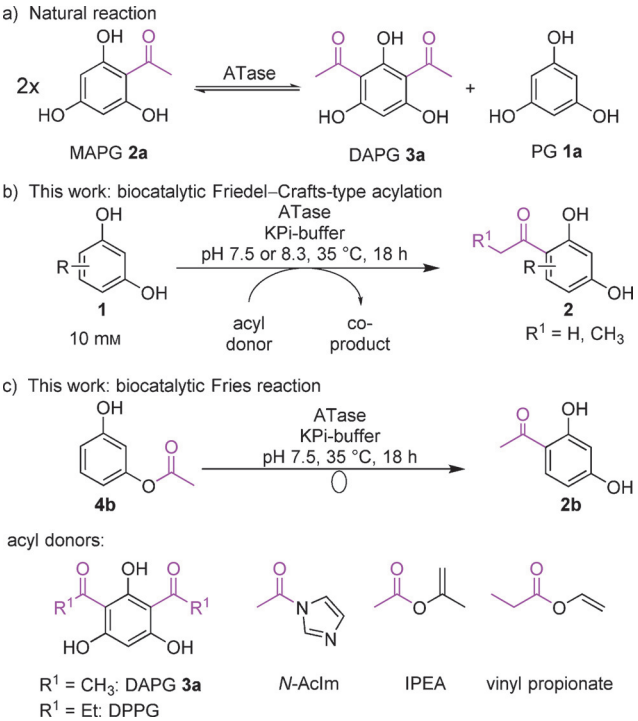
Abstract: *The Friedel–Crafts acylation is commonly used for the synthesis of aryl ketones, and a biocatalytic version, which may benefit from the chemo- and regioselectivity of enzymes, has not yet been introduced. Described here is a bacterial acyltransferase which can catalyze Friedel–Crafts C-acylation of phenolic substrates in buffer without the need of CoA-activated reagents. Conversions reach up to >99%, and various C- or O-acyl donors, such as DAPG or isopropenyl acetate, are accepted by this enzyme. Furthermore the enzyme enables a Fries rearrangement-like reaction of resorcinol derivatives. These findings open an avenue for the development of alternative and selective C–C bond formation methods.*

The direct C-acylation of aromatic compounds to form a new C–C bond was reported as early as 1873[1] and provided the basis for one of the most famous name reactions in organic chemistry: the Friedel–Crafts acylation.[2] More than fourteen decades later, this approach for forming C–C bonds endures as the standard method to prepare a broad range of aromatic ketones, and especially C-acylated phenols,[3] by employing various types of catalysts.[4] While Friedel–Crafts alkylations of non-natural substrates have been reported to proceed by employing various types of enzymes,[5] including SAM-dependent methyltransferases,[6] prenyltransferases,[7] and artificial metalloenzymes,[8] biocatalysts have—to the best of our knowledge—not yet been implemented to mediate the Friedel–Crafts acylation of non-natural substrates. A biocatalytic-type of regio- and chemoselective Friedel–Crafts acylation would be especially desirable for the C-acylation of phenols, because this reaction often leads to competing O-acylation or/and C-polysubstitution, which leads to product mixtures consisting of various isomers of the hydroxyphenyl ketones.[9] The latter, for example, are motifs in many fine chemicals and natural products.[10]

Recently, a multicomponent acyltransferase (ATase) isolated from the bacterium *Pseudomonas* sp. YGJ3 was shown to catalyze the reversible acetylation of monoacetylphloroglucinol [MAPG (**2a**), Scheme 1a] into phloroglucinol [PG (**1a**)] and the antibiotically active polyketide 2,4-diacetylphloroglucinol [DAPG (**3a**)] in a divergent reaction.[11] Thereby a nine-gene *phl* cluster encodes the biosynthetic machinery for DAPG production.[12] Unlike most other acyltransferases,[13] the heterotrimeric complex showing ATase activity (which is encoded by the conserved gene set *phlACB*) functions independently of CoA-activated substrates. Thus, this enzyme has properties which may be useful for catalyzing the direct C-acylation of non-natural phenol derivatives.



Scheme 1. Reactions catalyzed by acyltransferases from *Pseudomonas fluorescens*. a) Natural reaction: disproportionation of monoacetylphloroglucinol [MAPG (**2a**)] into 2,4-diacetylphloroglucinol [DAPG (**3a**)] and phloroglucinol [PG (**1a**)]. Non-natural reactions involve: b) The Friedel–Crafts bioacylation of resorcinols (**1**) into the corresponding aryl ketones **2** by using various acyl donors. c) Enzymatic Fries rearrangement-like reaction of phenolic esters (**4**) to give aryl ketones (**2**) as exemplified by the rearrangement of **4b** into **2b**.

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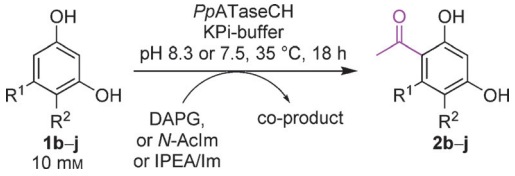
We initiated our investigations with a BLAST search using the *phlACBDEFGHI* gene cluster sequence of *Pseudomonas* sp. YGJ3[11a] as a template, and it revealed three *Pseudomonas* strains which harbor the hetero-trimeric ATase-encoding genes *phlACB*: *Pseudomonas brassicacearum* DSM 13227 with 80% identity, *Pseudomonas protegens* DSM 19095, and *Pseudomonas fluorescens* Pf-5 ATCC BAA-477 both having 99% identity to *Pseudomonas* sp. YGJ3. After initial tests (see Figure S1 and Table S2 in the Supporting Information) the ATase gene sequences encoding open-reading frames were engineered by matching the codon frequency of the wild-type *P. protegens* DNA with *E. coli*,[14] and by inserting ribosomal binding sites upstream of each of the *phl* genes from that bacterium. The cell-free extracts produced by this improved construct (*Pp*ATaseCH) had fivefold higher activities compared to analogous preparations derived from wild-type sequences (see Figure S1 and Table S2).

By testing various resorcinol derivatives (**1**), it was found that they can be converted using DAPG as the acetyl donor (Table 1). For example, compounds bearing a substituent at position 4 [like 4-chlororesorcinol (**1c**)] were acetylated with 98% conversion within 18 hours at 10 mM concentration to yield the mono-C-acetylated product **2c**. Interestingly, while a substrate with a methyl substituent at C4 (**1d**) underwent lower conversion (46%) under these reaction conditions, the bioacetylation of substrates having a longer alkyl chain in this position—ranging from ethyl (**1e**), 2-propyl (**1f**), *n*-butyl (**1g**), to *n*-hexyl (**1h**)—again produced either 98% conversion or went to completion.

Table 1: Regioselective *Pp*ATaseCH-catalyzed C-acetylations of non-natural resorcinol-derived acceptor substrates.



Substr.[a]	R^1	R^2	Yield [%][a] DAPG (**3a**)	*N*-AcIm	IPEA/Im
1b	H	H	97	41	88 (68)
1c	H	Cl	98	56	95 (95)
1d	H	CH_3	46	16[b]	29[b] (16)
1e	H	C_2H_5	98	48	87 (82)
1f	H	2-propyl	>99	54	98 (81)
1g	H	nC_4H_9	>99	62	98 (80)
1h	H	nC_6H_{13}	>99	97	84 (52)
1i	CH_3	H	3	n.d.	2 (n.p.)
1j	OMe	H	41	12	18 (10)

[a] Donor concentrations: DAPG (15 mM), *N*-AcIm (250 mM), IPEA (100 mM) with imidazole (100 mM); donor concentrations have been optimized for *N*-AcIm and IPEA/imidazole. See Methods for representative procedures. In case of DAPG the reaction mixture contained DMSO (10 vol.%). Conversions were determined by HPLC according to standard curves derived from authentic samples. The values represent the mean of two experiments. Values within parentheses refer to yields of isolated products. [b] In addition to **2d**, remaining O-acetylated product was also detected by HPLC. n.d. = not detected, n.p. = not performed.

Substrates with a substitution at C5 of the resorcinol core structure were also accepted, although a methyl group (**1i**) led to low conversion, and methoxy-substituted resorcinol (**1j**) was transformed with 41% conversion (Table 1). Notably, only C-acetylation was observed, thus leading to a single product with the acetyl group in the *ortho*- and *para*- position with respect to the OH moieties of the resorcinol core.

Substrates such as phenol or those with two OH groups in either the 1,2- (catechol) or 1,4-positions (hydroquinone), and resorcinol derivatives with substituents at C2 (chloro or methyl), were not converted.

While the interconversion of the native substrate MAPG (**2a**) into DAPG (**3a**) and PG (**1a**) is a reversible reaction, the bioacetylation of the resorcinols **1b–j** with the C-acyl donor DAPG proved to be irreversible, thus, the products **2b–j** did not act as acetyl donors.

However, since DAPG is not commercially available, alternative (inexpensive) acyl donors are highly desired. Testing compounds with a cleavable/hydrolyzable C–C-bond, such as acetylacetate and related 1,3-diketones, did not lead to a hit.

Serendipitously, we found that the activated amide *N*-acetylimidazole (*N*-AcIm) leads to C-acetylation of **1b** to give the product **2b** in the presence of *Pp*ATaseCH. In the absence of the enzyme, only O-acetylation of the substrate to the corresponding mono- and diesters, **4b** and **5b**, respectively, was observed as a spontaneous reaction, and **2b** was not detected (Figure 1). Monitoring the progress of the acetylation of **1b** with *N*-AcIm over time revealed that **4b** and **5b** are also formed in the presence of the enzyme, but these co-products were only detected in the initial phase of the acetylation (Figure 1; blue and dark blue lines).

While the spontaneously formed **5b** was transformed additionally (spontaneously hydrolyzed to **4b**), at the same rate in either the presence or absence of ATase (solid and dashed line), **4b** was transformed 1.6 times faster in the presence of the enzyme than in its absence. To determine the fate of this O-acetylated product in the enzymatic reaction, **4b** was synthesized and subjected to transformation with

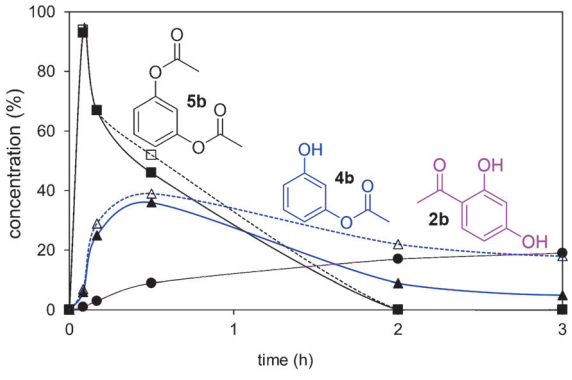
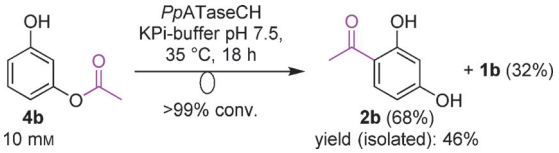


Figure 1. Time progression curves for the overall *Pp*ATaseCH-catalyzed acetylation of **1b** (10 mM) with *N*-AcIm (250 mM). Reaction was monitored in the presence (solid lines, filled symbols) and absence (dashed lines, open symbols) of the enzyme. The relative amounts of the product **2b** (magenta, ●), monoester **4b** (blue, ▲), and diester **5b** (dark blue, ■) were determined by HPLC. Symbols represent the mean of two ($n = 2$) experiments.

*Pp*ATaseCH. Although hydrolysis leading to the formation of **1b** (32%) was observed, apparent rearrangement of **4b** into **2b** (68%) was the main reaction (Scheme 2), and followed an intermolecular pathway (see the Supporting Information). Formally, this represents a biocatalytic equivalent to the Fries rearrangement,[15,16] which is generally promoted by stoichiometric amounts of Lewis acids at elevated temperatures.



Scheme 2. *Pp*ATaseCH-catalyzed Fries rearrangement-like reaction of resorcinol monoacetate (**4b**) by C–O cleavage and C–C bond formation to give **2b**.

Comparing the reaction rates for the formation of **2b** revealed that the enzymatic Fries-type rearrangement of **4b** proceeded three times faster than the overall Friedel–Crafts bioacetylation of **1b** with *N*-AcIm (Figures 1 and 2; magenta

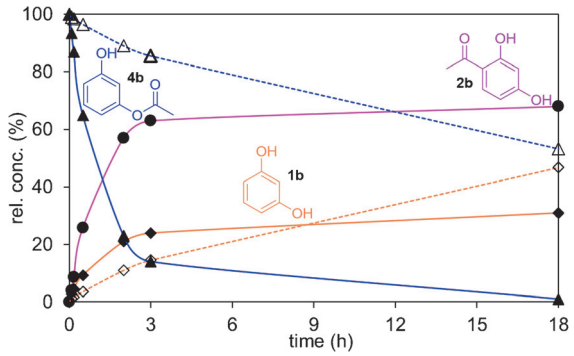


Figure 2. Time course of the *Pp*ATaseCH-catalyzed bio-Fries reaction of **4b** (10 mM) to give **2b**, and spontaneous hydrolysis of **4b** leading to **1b**. Reaction was monitored in the presence (solid lines, filled symbols) and absence (dashed lines, open symbols) of enzyme. The relative amounts of **2b** (magenta, ●), monoester **4b** (blue, ▲), and **1b** (orange, ◆) were determined by HPLC. Symbols represent the mean of two ($n=2$) experiments.

line). The rearrangement of **4b** into **2b** reached 68% product formation at a 10 mM substrate concentration within 18 hours, while the corresponding bioacetylation of **1b** with the N-acyl donor *N*-AcIm only achieved 41% (Table 1, entry 1 and Scheme 2). The data indicate, that spontaneous O-acetylation by *N*-AcIm and subsequent enzymatic Fries reaction is the predominant pathway for conversion of **1b** into **2b**, and is in contrast to DAPG/MAPG for which no O-acetylation was detected.

When we tested *N*-AcIm as a donor with the substrates **1c–j** (10 mM), we obtained only moderate conversions (Table 1), except for **1h** (97%). Consequently, our search for a more suitable donor continued.

Considering that an ester bond was cleaved during the Fries rearrangement-like reaction of **4b**, we investigated activated esters as possible acetyl donors. Indeed, enol esters such as vinyl acetate and isopropenyl acetate (IPEA), which are commonly employed in lipase reactions,[17] were accepted by the ATase as O-acetyl donors.[18] With a tenfold excess of either IPEA or vinyl acetate (100 mM), low amounts of **2b** were detected upon incubation with *Pp*ATaseCH after 18 hours (36% for vinyl acetate; 23% for IPEA). Interestingly, when the reactions were performed in the presence of equimolar amounts of imidazole (Im), the conversion improved to 55% for vinyl acetate and to 93% for IPEA (18 h; Figure 3).

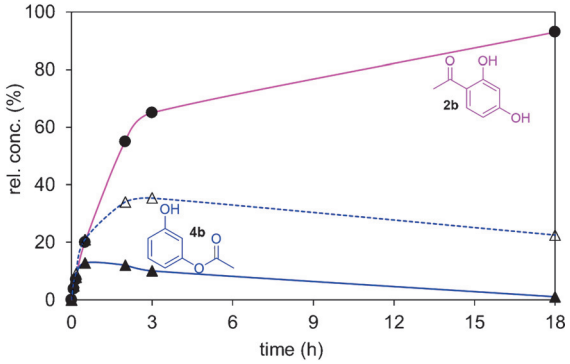


Figure 3. Time course of the *Pp*ATaseCH Friedel–Crafts bioacetylation of **1b** (10 mM) with IPEA (100 mM) in the presence of imidazole (100 mM). Reaction was monitored in the presence (solid lines, filled symbols) and absence (dashed lines, open symbols) of enzyme. The relative amounts of product **2b** (magenta, ●) and monoester **4b** (blue, ▲) were determined by HPLC. The missing amount corresponds to the concentration of **1b**.

Like *N*-AcIm, IPEA reacted spontaneously with **1b** to yield some **4b**, but in this case, **5b** was not observed at all. In the absence of imidazole, formation of **4b** with IPEA was low without the enzyme and barely detectable in the presence of the enzyme (see Figure S3). By employing imidazole as an additive (Figure 3), formation of **4b** with IPEA reached 34% in the absence of the enzyme, and is comparable with result from using *N*-AcIm (39%; Figure 1). However, in the presence of the enzyme formation of **4b** was just 13% at its maximum (Figure 3). The concentration of **4b** increased within the first hours of the reaction, most likely before **4b** underwent either a Fries rearrangement-like reaction to give **2b** or hydrolysis. Since the formation of **2b** in the presence of IPEA does not go in hand with significant formation of **4b**, as observed in the reaction with *N*-AcIm (Figure 1), it may indicate, that in the case of IPEA/imidazole the acetyl moiety is also transferred by a pathway other formation of **4b** by O-acetylation and rearrangement. In comparison, when using DAPG as a donor, the formation of **4b** was never observed at all (neither in the presence nor absence of the enzyme; see Figure S4). The experiments with DAPG suggest that the enzymatic C-acetylation does not necessarily require an O-acetylated substrate/intermediate such as **4b**.

The improved acetylation protocol using IPEA/Im was applied to the substrates **1b–j**, and this produced significantly higher conversions compared to using *N*-AcIm as the donor (Table 1). To confirm these products on a semi-preparative

scale, the bioacetylation of **1b–h** and **1j** was performed for tenth-gram quantities using commercially available IPEA as the donor in the presence of imidazole, thus achieving yields of up to 95% for these reactions when run for 24 hours (see the Supporting Information). We also confirmed the enzymatic Fries product of **4b** into **2b** on a semi-preparative scale [46% yield (isolated), Scheme 2]. It is worth mentioning, that the catalyst loading in comparison to the substrate was just 0.05 mol%.

We examined the ability of ATase to transfer acyl groups other than acetyl by testing the propanoyl analogues of MAPG (**2a**) and DAPG (**3a**). Di- and monopropanoylphloroglucinol (DPPG/MPPG, 15 mM) were readily accepted as donors for the transformation of **1b** (10 mM), thus yielding the respective C-monopropanoylated product **6b** with 69% (for DPPG) and 50% (for MPPG) conversion after 18 hours (Scheme 1b). Employing vinyl propionate as donor for the C-acylation of **1b**, using the same reaction conditions as with IPEA/Im, resulted in the formation of 14% of **6b** within 18 hours. However, larger acyl groups (like *n*-butanoyl) were not transferred by this transferase.

Summarizing, the regioselective C-acylation of resorcinol derivatives has been demonstrated using a biocatalyst and readily available IPEA in buffer. The presented biocatalytic Friedel–Crafts acylation method and, to the best of our knowledge, the first preparative biocatalytic equivalent to the Fries rearrangement[19] may open an avenue for the extension of the biocatalytic toolbox for C–C bond formation methods[20,21] to be applied in organic synthesis and biotechnology.

Experimental Section

General procedure for the Friedel–Crafts bioacetylations of **1b–h** and **1j** on semi-preparative scale: The acceptor **1b–h** or **1j** (10 mM final concentration) was dissolved in potassium phosphate buffer (50 mM, pH 7.5) in a baffled shaking flask. Imidazole (100 mM, added from a 1M stock solution prepared in the reaction buffer) was subsequently added. The mixture was preheated to 35°C for 10 minutes. Meanwhile, cell-free extract containing the *Pp*ATaseCH (165 U, 3.1 μM) was thawed at 21°C, followed by a short preheating period (35°C, 10 min). The enzyme solution was added to the reaction mixture and the bioacetylation was started by adding IPEA (100 mM final concentration). The bioacetylation (100 mL total volume, final pH 8.30) was run at 35°C and 140 rpm for 24 h. The reaction was aborted by acidification (pH ≈1.0) with aq. HCl (6 N) and shaking was continued for further 10 minutes to precipitate protein. The resulting suspension was extracted with CH_2Cl_2 (3×50 mL). The organic layers which still contained imidazolium salt and/or protein precipitate were centrifuged (15 min, 14000 rpm) to remove the remaining solids. The cleared organic layers were pooled in a separation funnel, washed with brine (2×40 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography. Compounds were characterized by ^1H and ^{13}C NMR spectroscopy and GC-MS, and the chemical identity was confirmed by comparison to literature data (see the Supporting Information).

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Conflict of interest

The authors declare no conflict of interest.

Keywords: acylation · arenes · biocatalysis · enzymes · rearrangements

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