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Flavin Catalysis Employing an N(5)-Adduct: An Application in the Aerobic Organocatalytic Mitsunobu Reaction

Michal März,[a] Martin Babor,[b] and Radek Cibulka*[a]

Abstract: An artificial flavin system has been firstly proved to employ an N(5)-adduct for a catalytic transformation. This mode of catalysis occurs in some flavoenzymes but it is unknown in chemocatalysis, still exclusively using only C(4a)-adducts. In our report, an ethylene-bridged biomimetic flavin has been shown to participate in the Mitsunobu esterification reaction as an alternative to dialkyl azodicarboxylate. The reaction occurs via a flavin N(5)-triphenylphosphine adduct and is catalytic from the point of view of the flavin, which is regenerated by oxygen. This approach distinguishes from other catalytic Mitsunobu reaction procedures which always need an extra catalytic system.

There are over a thousand flavoenzymes recognized today and a large number of them have been evaluated in terms of their structure and/or mechanism of action.[1,2] In flavoenzymes, the flavin co-factors (FMN or FAD) participate in one- or two-electron redox processes via an electron transfer. In addition, covalent adducts of the flavin species with the substrate and/or reagent play an essential role in many transformations.[2a,3] In particular, the adducts formed at the C(4a) position of the flavin (**Fl**) core are important intermediates (see Figure 1). For example, flavin-4a-hydroperoxide is a versatile agent in monooxygenases[4] and the corresponding thiol adduct is an intermediate of glutathione reductase.[5] The N(5) position of the flavins is also important in enzymatic processes; however, it is mainly involved in hydrogen atom transfer. According to the current literature, the formation of an adduct at the N(5) position with species other than hydride is limited to the carbanions in nitroalkane oxidase[6] and acyl dihydroxyacetone-P synthase, respectively.[7]

Artificial systems using flavinium salts **1** or **2** have been used to mimic the functions of flavin co-factors as well as to help to understand the mechanism of the transformations occurring in flavoenzymes.[8,9] Moreover, some catalytic processes based on flavinium salts have been established as valuable tools in organic synthesis.[8,9] In contrast to flavoenzymes, only the C(4a) adducts have been described in these artificial catalytic systems. This is natural for 5-alkylflavinium salts **1** with a covalently blocked N(5) position.[4,8a,b] However, also catalytic processes using ethylene-bridged flavinium salts **2** bearing a free N(5) position have been described to occur exclusively through their corresponding 10a-adduct (Figure 1).[9a,10] The only artificial flavin N(5) adduct reported to date is **2a-PPh$_3$**, which was reported by Müller and shown to be reversibly formed from **2a** and triphenylphosphine (Ph_3P).[11]

Herein, we report the unprecedented application of a flavin N(5)-adduct in artificial catalysis. Specifically, the N(5)-adduct of **2** and triphenylphosphine was shown to activate alcohol during the esterification of a carboxylic acid to provide its corresponding ester in an analogous manner to the Mitsunobu reaction. It should be noted that the conventional Mitsunobu esterification protocol needs stoichiometric amounts of both triphenylphosphine and dialkyl azodicarboxylate, and produces a large quantity of the triphenylphosphine oxide and dialkyl hydrazine dicarboxylate by-products.[12] This fact together with the explosive character of dialkyl azodicarboxylates are disadvantages of the Mitsunobu reaction in large-scale. In our protocol, the conventional stoichiometric dialkyl azodicarboxylate reagent was replaced by a catalytic amount of a biomimetic flavin, which is regenerated *in situ* by oxygen (Scheme 1A). To the best of our knowledge, our procedure is the first organocatalytic Mitsunobu reaction protocol in which the Mitsunobu reagent is regenerated directly with oxygen without the need of any additional reagents. A few catalytic procedures with either dialkyl azodicarboxylate or phosphine regeneration have been previously reported.[13,14] However, they require at least an extra catalyst or even a sacrificial oxidizing (other than oxygen) or reducing agent (Scheme 1A, left).

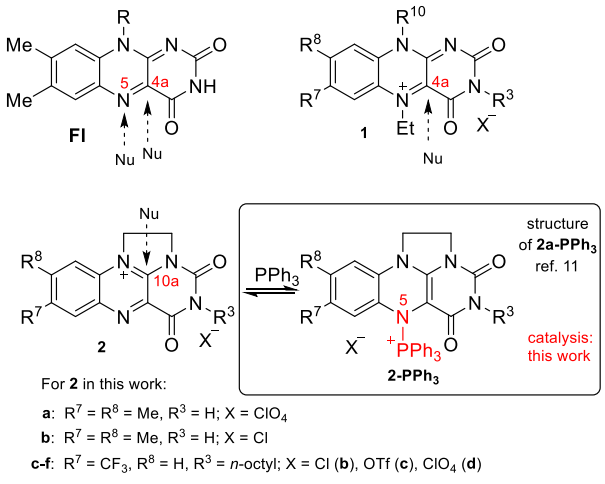

Figure 1. Structure of flavin cofactors (**Fl**; e.g. R = ribityl for riboflavin, R = ribitol-5-phosphate for flavinmononucleotide) and flavinium salts **1** and **2** and schematic formation of adducts with nucleophiles (**Nu**). The artificial flavin N(5)-adduct[11] (in box).

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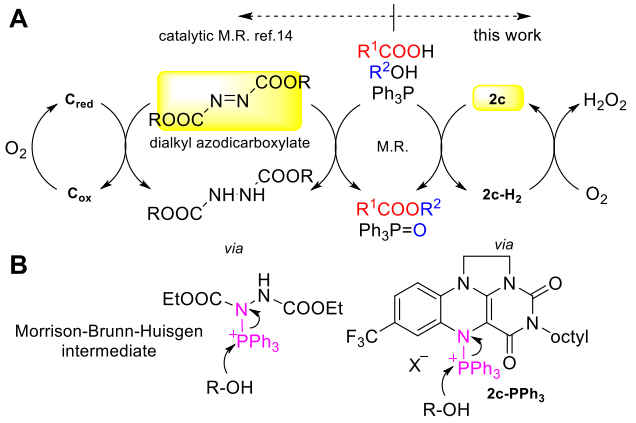
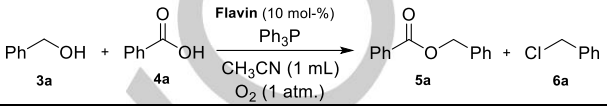


Scheme 1. Mitsunobu reaction (M.R.) procedure with catalytic amount of dialkyl azodicarboxylate regenerated by oxidation catalysed by **C** (A, left) and flavin-catalysed esterification presented in this work (A, right). Intermediates are shown in (B).

The structure of complex **2-PPh₃** is remarkably similar to the Morrison-Brunn-Huisgen intermediate formed during conventional Mitsunobu reaction from dialkyl azodicarboxylate and triphenylphosphine (Scheme 1B). Therefore, we envisage its use in the catalytic Mitsunobu reaction. In such procedure, **2-PPh₃** would react with alcohol to give the corresponding alkoxy triphenylphosphonium intermediate (i.e., the alcohol hydroxyl group is activated towards the nucleophilic substitution reaction) and dihydroflavin **2-H₂**. Consequently, dihydroflavin **2-H₂** would be oxidized using molecular oxygen to regenerate flavinium salt **2** for the next catalytic cycle (cf. Scheme 2).[15] We have proven this concept using the model reaction between benzyl alcohol **3a** and benzoic acid **4a**. Using 10 mol% of flavin **2b** (the chloride salt of 7,8-dimethylflavinium used by Müller) and 2.0 equivalents of Ph_3P, ester **5a** was formed in 13% conversion (Table 1, Entry 1). We hypothesized the electron density on the flavin subunit will affect the formation and reactivity of the adduct. Indeed, the use of 7-trifluoromethylflavinium chloride **2c** significantly increased the yield of the target ester (Table 1, Entry 2). Further optimization was focused on the structure of phosphines. However, reactions with triarylphosphines possessing an electron-donating ((4-MeOPh)$_3$P) or an electron-withdrawing group ((4-ClPh)$_3$P) gave significantly lower amount of ester compared to those with Ph_3P. Reaction with aliphatic phosphines (tributyl- and tricyclohexylphosphine) does not provide ester at all (see Supporting Information). It should be noted that changing the solvent did not improve the reaction yield (see Supporting Information). On the other hand, an excess of Ph_3P, elevated temperature and longer reaction time increased the amount of ester formed in our catalytic procedure (Table 1, Entries 3-7). Molecular sieves (MS) were essential in the reaction (Table 1, Entry 14) as decomposed the hydrogen peroxide formed from oxygen during the regeneration of the flavin catalyst. It was proved by an independent experiment with classical Mitsunobu reaction which does not proceed when hydrogen peroxide (1 equiv.) is added. On the other hand, esterification started immediately after addition of MS to the reaction mixture containing hydrogen peroxide. Notably, a small amount of chloride **6a** was formed from the alcohol involving the anion of the flavinium catalyst via a nucleophilic substitution reaction. This could be eventually eliminated using a flavinium catalyst containing a non-nucleophilic anion, e.g., flavinium triflate **2d** or perchlorate **2e** (Entries 8-9). Importantly, the formation of ester **5a** was not observed in the blank experiment (i.e. in the absence of either **2** or triphenylphosphine) (Table 1, Entries 11 and 12). In addition, the reaction did not occur when a neutral flavin, 3-methyl tetraacetyl riboflavin (**7**), was used instead of flavinium salt **2** (Entry 10), which was attributed to the weak interactions between **7** and Ph_3P.[16]

Table 1. Looking for conditions for aerial catalytic Mitsunobu reaction mediated by flavins.[a]

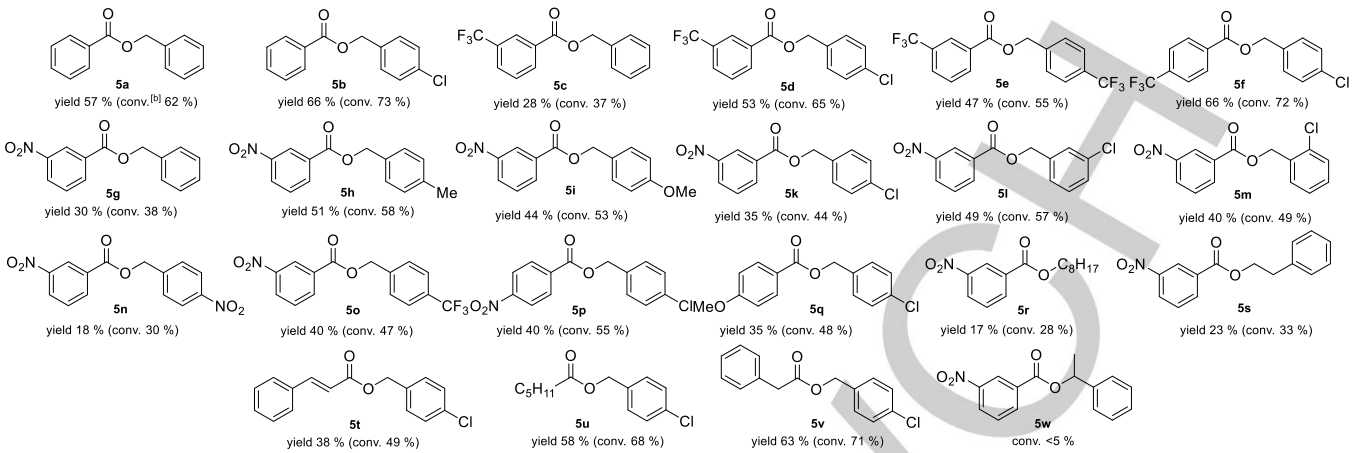


Entry	Flavin	Time [h]	Ph_3P [equiv]	Temp. [°C]	Yield[b] [%]	
					5a	**6a**
1	**2b**	24	2	25	13	3
2	**2c**	24	2	25	31	5
3	**2c**	24	2	50	39	6
4	**2c**	48	2	50	49	6
5	**2c**	24	2	60	31	4
6	**2c**	48	2.5	50	62	6
7	**2c**	48	3	50	59	7
8	**2d**	48	2	50	43	0
9	**2e**	48	2	50	40	0
10	**7**	24	2	50	0	0
11	-	24	2	50	0	0
12	**2c**	24	-	50	0	0
13	**2c**[c]	24	2.5	50	61	5
14[d]	**2c**	24	2	50	0	0

[a] Reaction conditions: **3a** (75 μmol), flavin (7.5 μmol), **4a** (90 μmol), MS 4Å (150 mg), oxygen (balloon). [b] Conversion was determined by ^{1}H NMR. [c] Added in the form of **2c-PPh₃** adduct. [d] No MS.

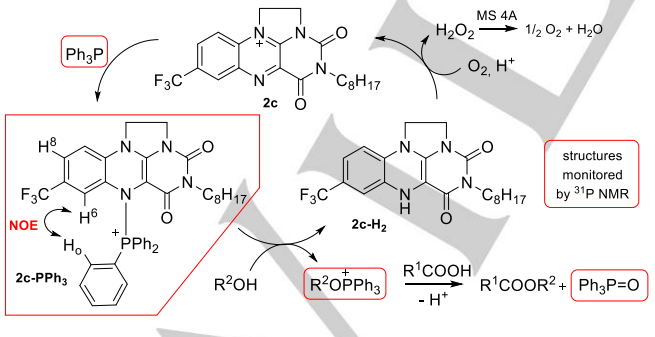
Using the optimal conditions in regards to the amount of ester formed, we investigated the substrate scope from the point of view of both the carboxylic acid and alcohol (Table 2). Chloride **2c** can be used as the catalyst as by-product **6** was found to be separable by column chromatography during the purification of the final ester product **5**. The ester products were formed in moderate to good yield with all the benzoic acid studied including unsubstituted substrates (**5a** and **5b**) and those substituted with electron-withdrawing (**5c**-**p**) or electron-donating (**5q**) groups. Various benzyl alcohols were also transformed into their corresponding esters irrespective of the type (**5b**-**i** and **5n**) and position (**5k** vs **5l** vs **5m**) of the substituent. Importantly, significant yields of the desired esters were formed in the case of aliphatic (**5u** and **5v**) and unsaturated acids (**5t**). The yields and conversions of the esters derived from aliphatic alcohols (**5r** and **5s**) were relatively small, but nevertheless, still sufficient to confirm the regeneration of the flavin catalyst. Unfortunately, we did not succeed with our attempt to prepare ester **5w** using 1-phenylethanol, which was attributed to the steric hindrance of the secondary alcohol.[17] It should be noted that esterification with 1 mmol of 4-chlorobenzyl alcohol (**3b**) and 1.2 mmol **4a** afforded ester **5b** in the yield 58% confirming the procedure is useful on preparative scale.

Table 2. Substrate scope for esterification mediated by **2c** catalyst and Ph_3P.[a]



[a] Reaction conditions: alcohol **3** (150 μmol), **2c** (15 μmol), acid **4** (180 μmol), Ph_3P (375 μmol), MS 4Å (300 mg), oxygen (balloon), 50 °C, 48h. [b] Determined by ^1H NMR.

Next, we turned our attention to the reaction mechanism, which is outlined in Scheme 2. Initially, we confirmed the formation of the adduct formed upon mixing flavinium salt **2c** and triphenylphosphine using ^1H NMR spectroscopy (see Figure 2). The stepwise addition of triphenylphosphine to a solution of **2c** in acetonitrile resulted in the decrease of the signals corresponding to **2c**, which completely disappeared when an excess of Ph_3P was present (**2c**:Ph_3P = 1:2). New signals corresponding to the flavin moiety appeared and were shifted in the direction of the signals observed for **2-H₂**, which indicated the "reduced" form of the flavin was present in the adduct. In addition, new signals of bound Ph_3P appeared in the spectrum and their chemical shift indicated a positive charge was present on the phosphorus atom. The structure of complex **2c-PPh₃** was further confirmed by HR-MS and the NOE observed between the *ortho*-hydrogen atoms on the phenyl ring in Ph_3P and the hydrogen atom at C(6) on the flavin moiety (see Scheme and Supporting Information). The adduct was also isolated as a solid.



Scheme 2. The proposed mechanism of esterification mediated by **2c** catalyst and Ph_3P. Anion is omitted for clarity.

Importantly, when monitoring the model esterification reaction of trifluorobenzoic acid and methanol in the presence of a substoichiometric amount of **2c** (0.25 equiv.) and PPh_3 (0.5 equiv.) using ^{31}P NMR spectroscopy, we observed a new signal at δ = 47.3 ppm corresponding to the signal of **2c-PPh₃** prepared in an independent experiment (Figure 3). This signal was located in the area typical for the Morrison-Brunn-Huisgen intermediate.[18] Moreover, another signal at δ = 63.5 ppm was present in the spectrum, which corresponded to the signal of a methoxytriphenylphosphonium species,[19] an intermediate of the Mitsunobu reaction (Figure 3). Notably, when adding **2c-PPh₃** (prepared in advance) into the catalytic esterification instead of **2c**, almost the same conversion of **3a** to **5a** was observed (see Table 1, entries 6 and 13).

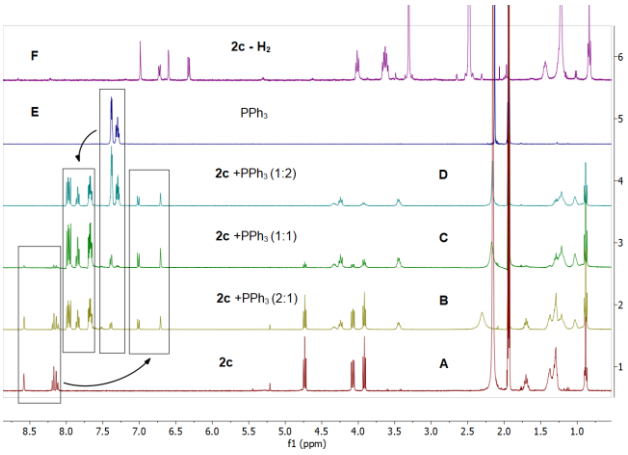


Figure 2. ^1H NMR spectrum of flavinium salt **2c** (5 mg) in the absence (spectrum A) and in the presence of PPh_3 (B-D) in CD_3CN (1 mL). Spectra of Ph_3P (E) in CD_3CN and reduced flavin **2c-H₂** (F) in DMSO-d6 are given for comparison.

We also used ^{31}P NMR spectroscopy to explain why the conversions of the alcohols to their corresponding esters was not quantitative. In standard experiments with catalytic amount of **2c**, triphenylphosphine oxide and the remaining triphenylphosphine, which was used in excess, were observed after 48 h of reaction. However, we never observed the signal corresponding to the **2c-PPh$_3$** adduct after finishing the reaction. This adduct should be detectable if **2c** is present along with PPh_3 in the reaction mixture (when considering the ease of adduct formation in the presence of Ph_3P). This indicated that the flavinium catalyst underwent an undesired decomposition pathway and the esterification reaction was stopped before achieving quantitative conversion. After the addition of another dose of catalyst **2c** after 48h, higher conversion (80%) of ester was formed according to an independent experiment.

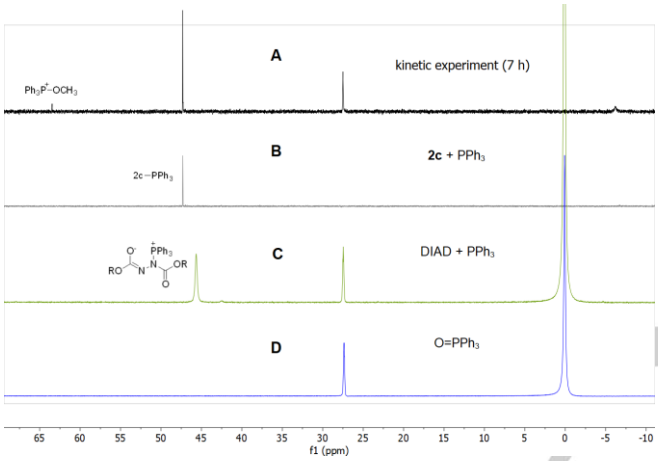


Figure 3. Selected ^{31}P NMR spectrum of model esterification of methanol (0.15 mmol) with 3-trifluoromethylbenzoic acid (0.15 mmol) in the presence of Ph_3P (0.075 mmol), **2c** (0.0375 mmol) and activated MS 4 Å (50 mg) in CD_3CN (1 mL) under oxygen after 7h heating at 50 °C (spectrum A). ^{31}P NMR spectrum of adduct **2c-PPh$_3$** (B), betain formed from DIAD and Ph_3P with signal of Ph_3P=O usually formed after mixing DIAD and Ph_3P (C), and Ph_3P=O (D) are given for comparison.

The Mitsunobu reaction is known to proceed via an S_N2 reaction on the activated alcohol by the triphenylphosphonium species. Nevertheless, the alkoxyphosphonium is often in an equilibrium with the acyloxyphosphonium species in the presence of the carboxylic acid.[12b,20] Thus, the carboxylic acid group could be activated towards the acyl substitution reaction. The contribution of both pathways was estimated to be 73:27 for the S_N2 vs S_NAc reaction in our case using the model esterification reaction between isotopically-labelled benzoic acid and benzyl alcohol (see Supporting Information). For comparison, the same transformation with stoichiometric amount of diisopropyl azodicarboxylate afforded exclusively product of S_N2 reaction.

Participation of S_N2 and S_NAc reaction pathway can be also recognized monitoring stereochemistry of esterification of chiral secondary alcohols. Unfortunately, as mentioned above (Table 2), we observed only traces of **5w** after esterification of 3-nitrobenzoic acid with 1-phenylethan-1-ol using catalytic procedure. Thus, we performed this esterification with stoichiometric amount of flavin **2c**. Interestingly, we isolated (*S*)-**5w** with the yield 28% and ee = 95% starting from (*S*)-1-phenylethan-1-ol. The observed retention can be explained that S_NAc pathway predominates in the reaction with secondary alcohols preferring activation of less sterically demanding (and more acidic) carboxylic group.

In conclusion, first catalytic system which employ N(5)-adduct to flavin species was developed in artificial catalysis. It confirms that this mode of flavin-based activation is possible also outside enzymes. Flavinium salt **2c** was shown to participate in the Mitsunobu esterification reaction as an alternative to dialkyl azodicarboxylate. In the presence of triphenylphosphine, **2c** forms the N(5) adduct, which is able to activate alcohols towards the esterification reaction with various carboxylic acids. Our procedure is catalytic from the point of view of the flavin and it is distinguishable from other catalytic Mitsunobu protocols[13,14] due to the direct regeneration of the Mitsunobu reagent by oxygen without the need of an additional catalytic system or sacrificial oxidant. Despite some limitations in substrate scope, this example clearly shows that the toxic and explosive dialkyl azodicarboxylates usually used in the Mitsunobu reaction could be replaced by environmentally benign biomimetic flavins. The structural modification of these flavin derivatives to improve their efficiency and substrate scope in this procedure is currently under investigation in our laboratory.

Experimental Section

See Supporting Information for experimental details.

Acknowledgements

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Keywords: Flavoenzymes • Organocatalysis • Flavins • Esterification • Mechanism

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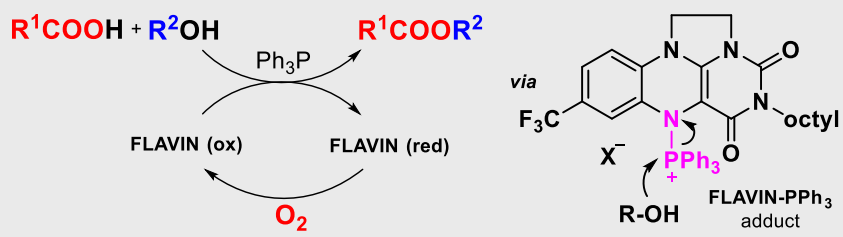
Key topic: Biomimetic organocatalysis

Layout 2:

COMMUNICATION



An N(5)-flavin adduct was firstly utilized in artificial catalysis! Adduct of a flavin derivative with triphenylphosphine provides catalytic Mitsunobu reaction in which flavin acts as Mitsunobu reagent instead of dialkyl azodicarboxylate. Flavin is used in catalytic amount only as it is regenerated by dioxygen.

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