

Controlling Acylation Regioselectivity with Photo-switchable Azo-Peptide Catalysts

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Group Seminar #402

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*“Beyond activity control: Throughout this review we have focused on catalytic activity, encoding the ability of the catalyst to enable and speed up an otherwise unfeasible chemical reaction. However, one of the inherent challenges in catalyst research is not only the mere enabling of a given chemical transformation **but also the complete control over its outcome by developing suitable catalysts to dictate chemoselectivity, regioselectivity, and stereoselectivity of the reaction.**”*

Reviews

S. Hecht and R. S. Stoll

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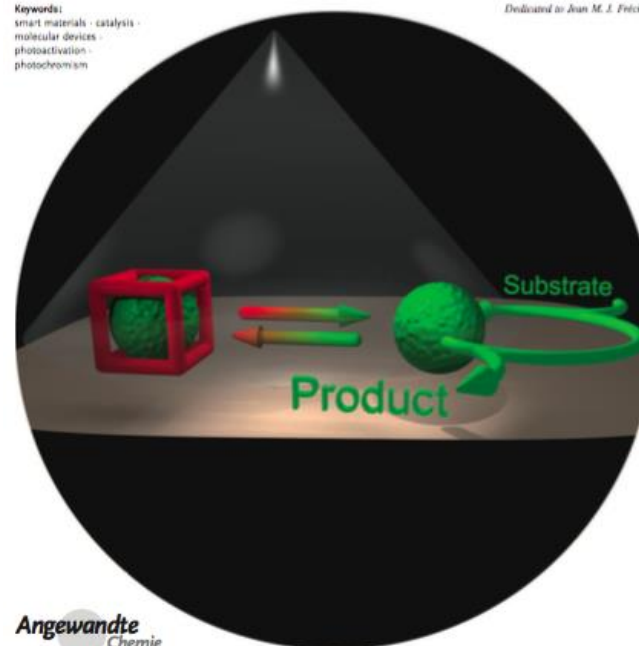
Photochemistry

Artificial Light-Gated Catalyst Systems

Ragnar S. Stoll and Stefan Hecht*

Keywords:
smart materials · catalysis ·
molecular devices ·
photoactivation ·
photochemistry

Dedicated to Jean M. J. Fréchet



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“Ultimately, photoswitchable catalysis will require the ability to photochemically alter the selectivity of the catalyst in addition to its activity. A system in which the catalyst’s intrinsic chemo-, regio-, and/or stereoselectivity could be remotely photomodulated will have numerous applications in tandem catalysis, and is expected to provide unprecedented control over polymer microstructure, as well as to simplify multistep syntheses of complex small molecules.”

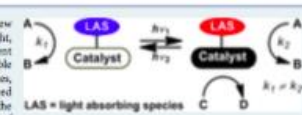
Illuminating Photoswitchable Catalysis

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ABSTRACT: Through the realization of conceptually new approaches aimed at controlling chemical reactions using light, the field of photoswitchable catalysis has seen rapid development over the past three decades. Although many photoswitchable catalysts are heterogeneous and utilize photosensitive surfaces, such as TiO₂ and CdSe, significant attention has also been directed toward homogeneous analogues, primarily by capitalizing on the steric changes that accompany the E⁺ ↔ Z photoisomerizations of azobenzene or stilbene derivatives. More recently, photochromic diarylethene moieties have been used to switch the intrinsic catalytic activities and selectivities through alteration of the steric and electronic properties displayed by a supporting ligand. In addition to detailing the aforementioned advances, this perspective summarizes other important developments in photoswitchable catalysis and offers a viewpoint on the future outlook of the field.

KEYWORDS: catalyst, photoswitchable, photochromism, azobenzene, diarylethene



■ INTRODUCTION

Many of the essential functions found in living organisms are controlled by molecular units that undergo changes triggered by external stimuli. Indeed, many biological systems harness externally applied energy and use it to regulate molecular transport or catalytic phenomena with exquisite spatial and temporal control. In contrast, synthetic chemical processes are typically limited to a fixed rate and/or selectivity once the reaction conditions are chosen. Incorporating stimuli-responsive units into synthetic processes may enable switchable catalytic activities and/or selectivities, and facilitate applications that range from streamlined multistep syntheses to the production of polymers with sophisticated microstructures.¹

Significant efforts in the field of catalysis have been directed toward the optimization of catalyst structure to achieve high substrate conversions and/or high regio-, chemo-, or stereoselectivities. More recently, however, efforts have focused on using external stimuli, including acid–base chemistry,² mechanical force,³ redox processes,⁴ and light⁵ to modulate the intrinsic activities and/or selectivities displayed by catalysts. Light, in particular, is an attractive stimulus as it is noninvasive, offers excellent temporal and spatial resolution, and can be precisely controlled with an appropriate source. Furthermore, using light of predetermined wavelengths allows for selective excitation and subsequent reactivity of specific molecular units in a highly controlled manner.

Photoreponsive processes found in nature, including photosynthesis and vision, illustrate the power of using electromagnetic radiation to initiate and regulate complex molecular and biochemical processes, and underscore the potential utility of synthetic catalysts that respond to light with similar precision. A number of conceptually different approaches have been used to realize artificial photoreponsive systems, including photocatalysis, photoactivated catalysis, and photoswitchable catalysis. In photocatalysis,⁶ an inactive

precatalyst is irradiated to generate a catalytically active, photoexcited state which subsequently reacts with a substrate (Figure 1a). In contrast, photoactivated or “photocaged” catalysis starts with an inactive catalyst species that, upon irradiation, becomes catalytically active (Figure 1b). Notable examples of photoactivated catalysis include photocaged and photobase generators,⁷ as well as metal complexes that become activated upon the dissociation of photolabile ligands.^{8,9} Photoswitchable catalysis involves a catalytically active species that undergoes a reversible photochemical transformation and, as a result, alters its intrinsic catalytic properties (Figure 1c). The catalyst in its initial state may be active or inactive, and the photoinduced transformation may either change the rate at which the catalyst facilitates a given reaction ($A \rightarrow B$; $k_1 \neq k_2$) or may allow the catalyst to promote a different reaction ($C \rightarrow D$). If the forward and reverse transformations are induced by orthogonal stimuli (i.e., different wavelengths of light), the catalyst may be toggled between two states that display different reactivities or selectivities via a remote light stimulus. Although more difficult to realize, photoswitchable catalysis offers distinct advantages over photocatalysis or photoactivated catalysis, since it adds the potential for controlling the catalyst as the reaction proceeds in addition to regulating the initiation process.

An ideal photoswitchable catalyst requires that the photoinduced transformation (i) occurs with high efficiency in both the forward and the reverse directions, (ii) causes a significant alteration in steric or electronic properties of the catalyst, and (iii) ultimately results in changes in catalytic activities and/or selectivities. Additionally, the photosensitive unit should be capable of absorbing light at a wavelength that will not excite

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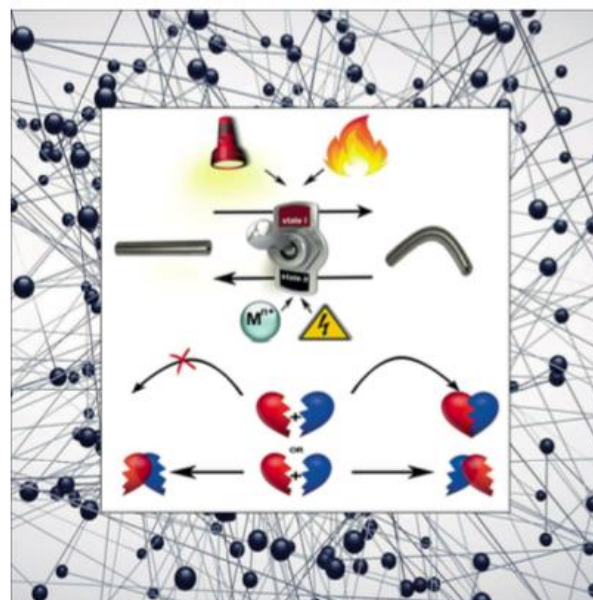


Even though progress in this field has been remarkable, **major barriers remain that need to be overcome**. For example, a photoswitchable catalyst capable of catalyzing two orthogonal reactions is yet to be reported. Unlike redox-switchable and ion-switchable systems, in which chemical waste is generated, **photoswitchable systems offer major advantages, as they use a clean and noninvasive external trigger that allows spatiotemporal precision**.

Switchable Catalysts

Dynamic Responsive Systems for Catalytic Function

Matea Vlatković, Beatrice S. L. Collins, and Ben L. Feringa^{*id}

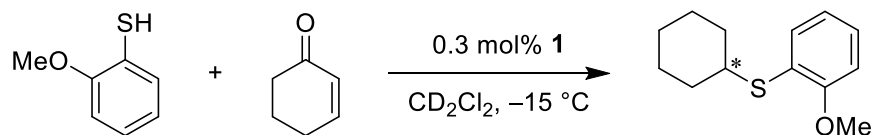
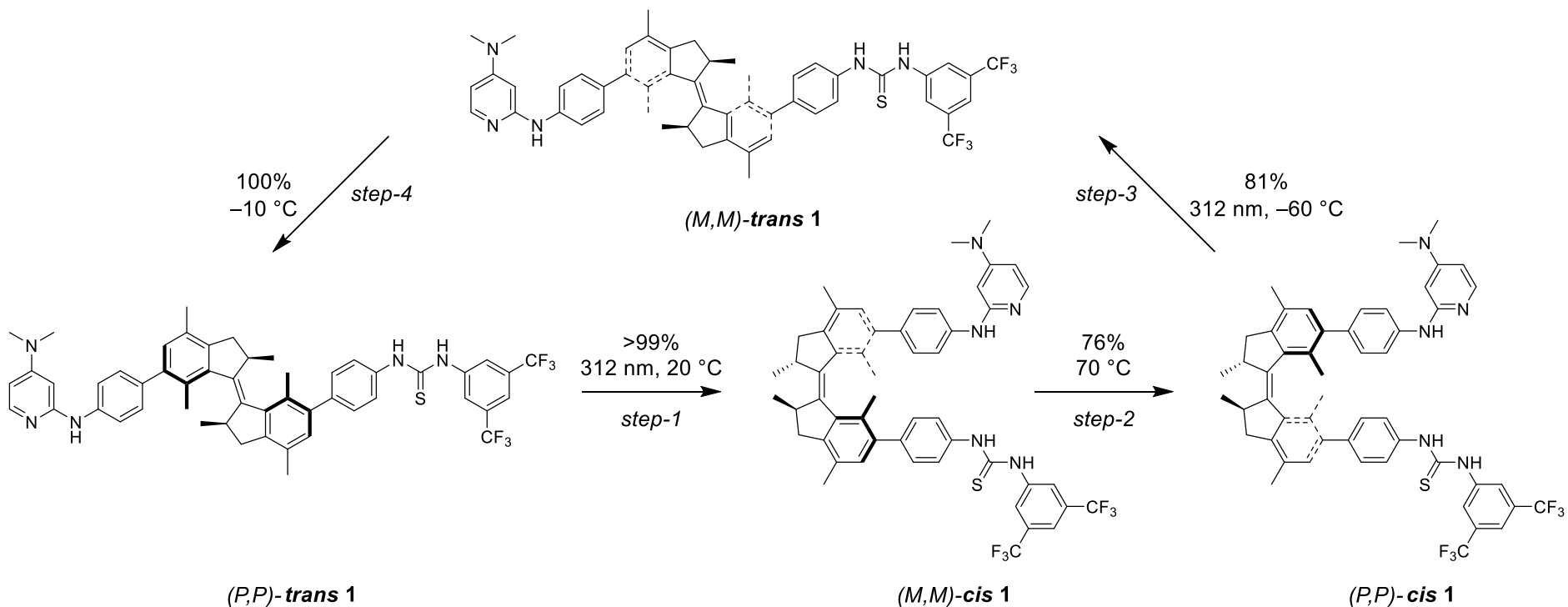


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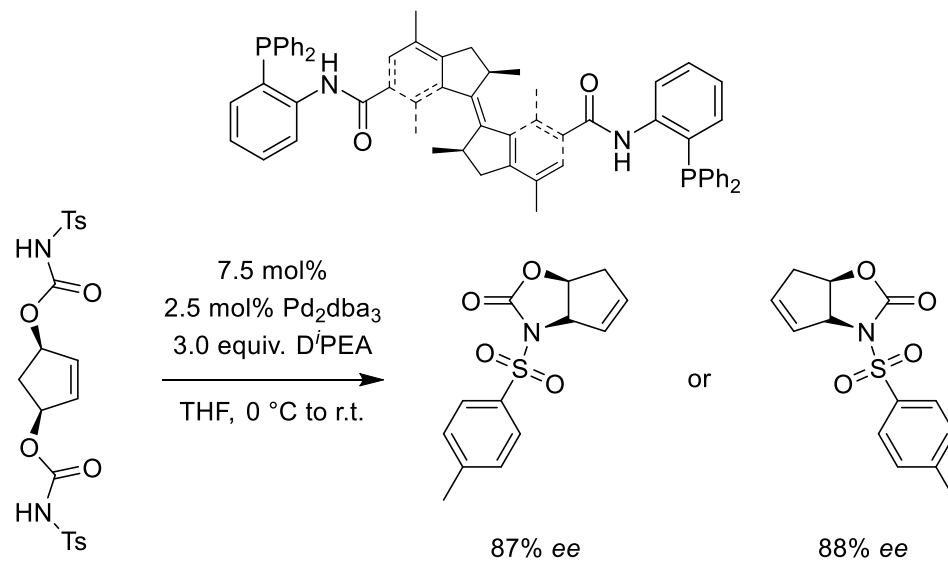
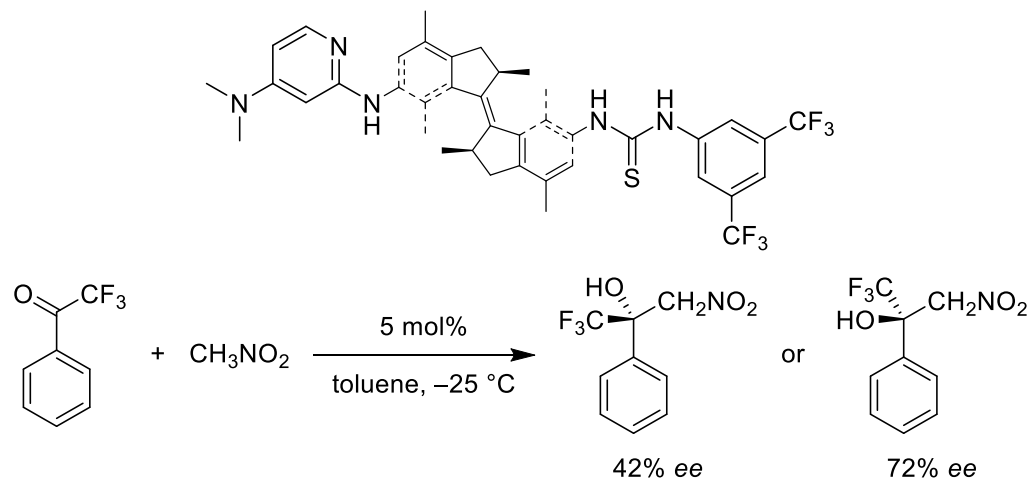
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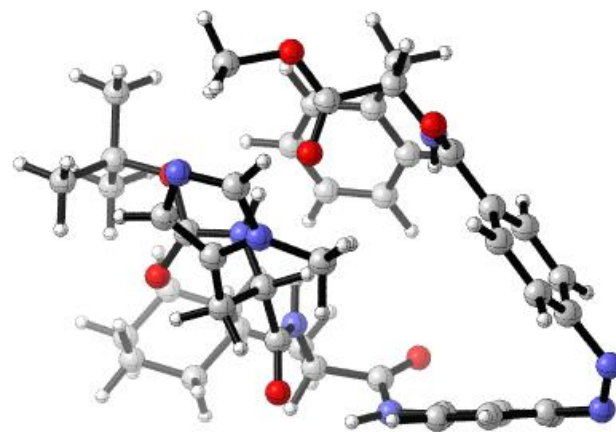
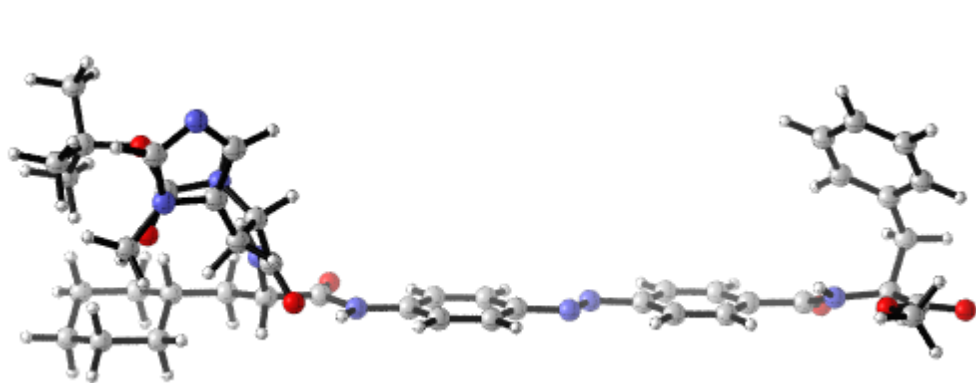
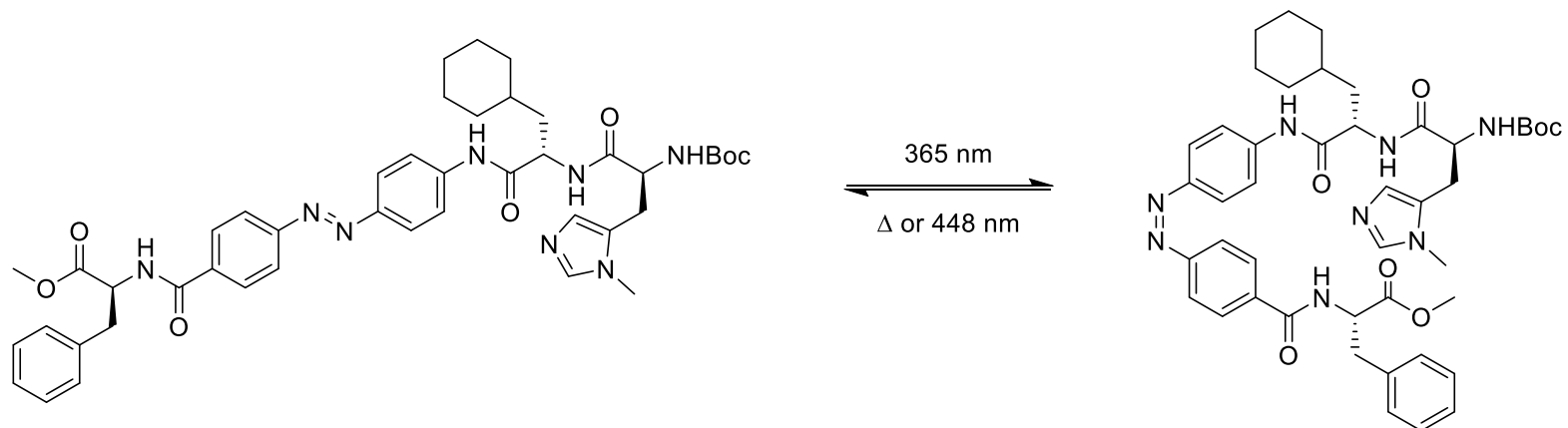
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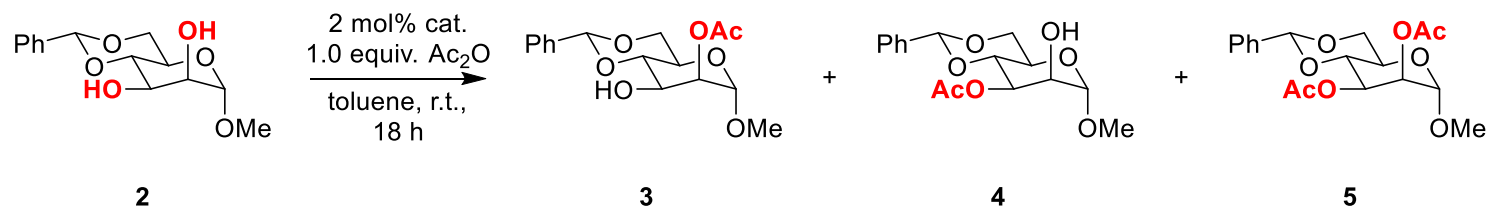


(P,P)-trans 1: rac.
(M,M)-cis 1: (*S*) 48% ee
(P,P)-cis 1: (*R*) 50% ee



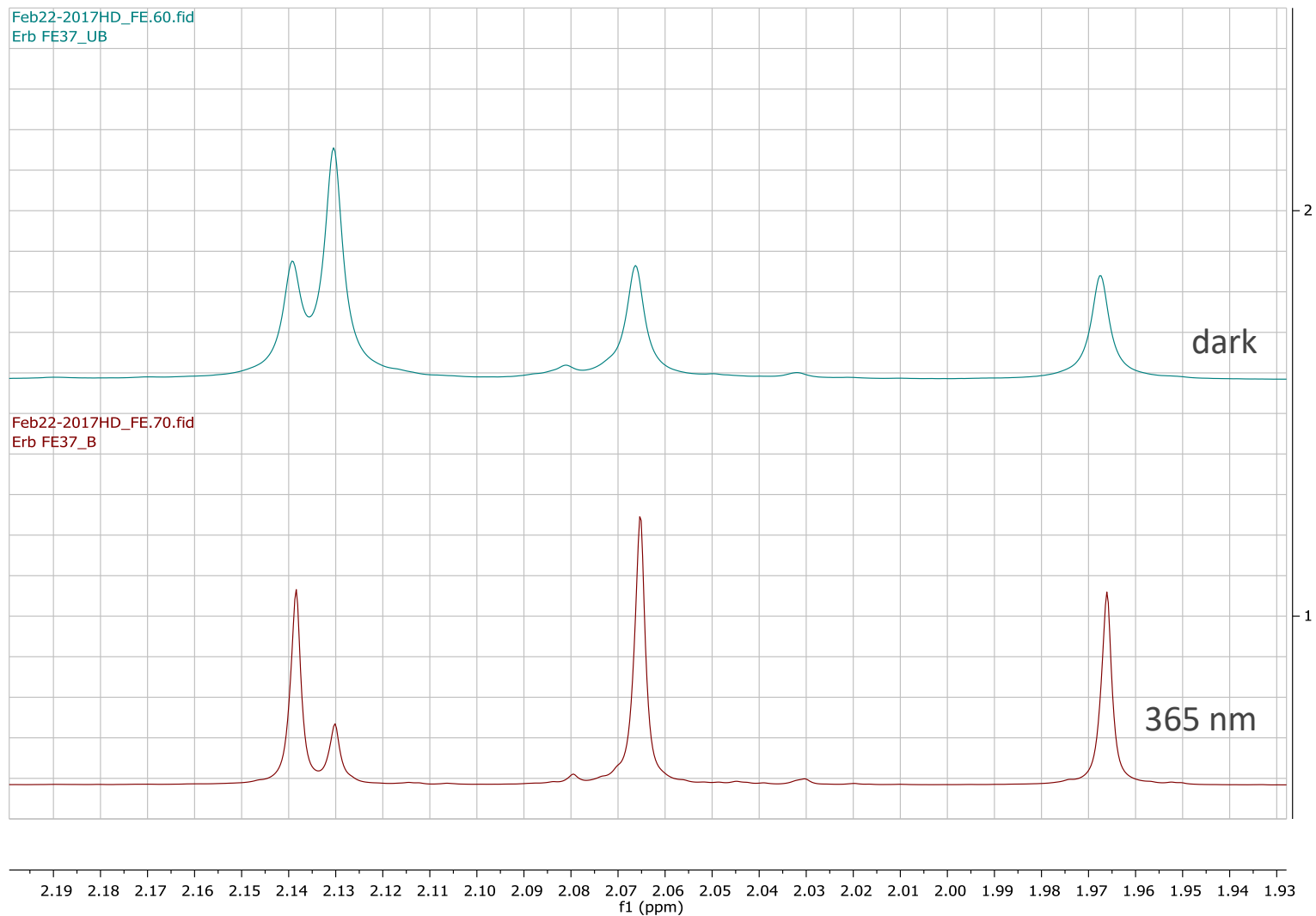


Fred_1

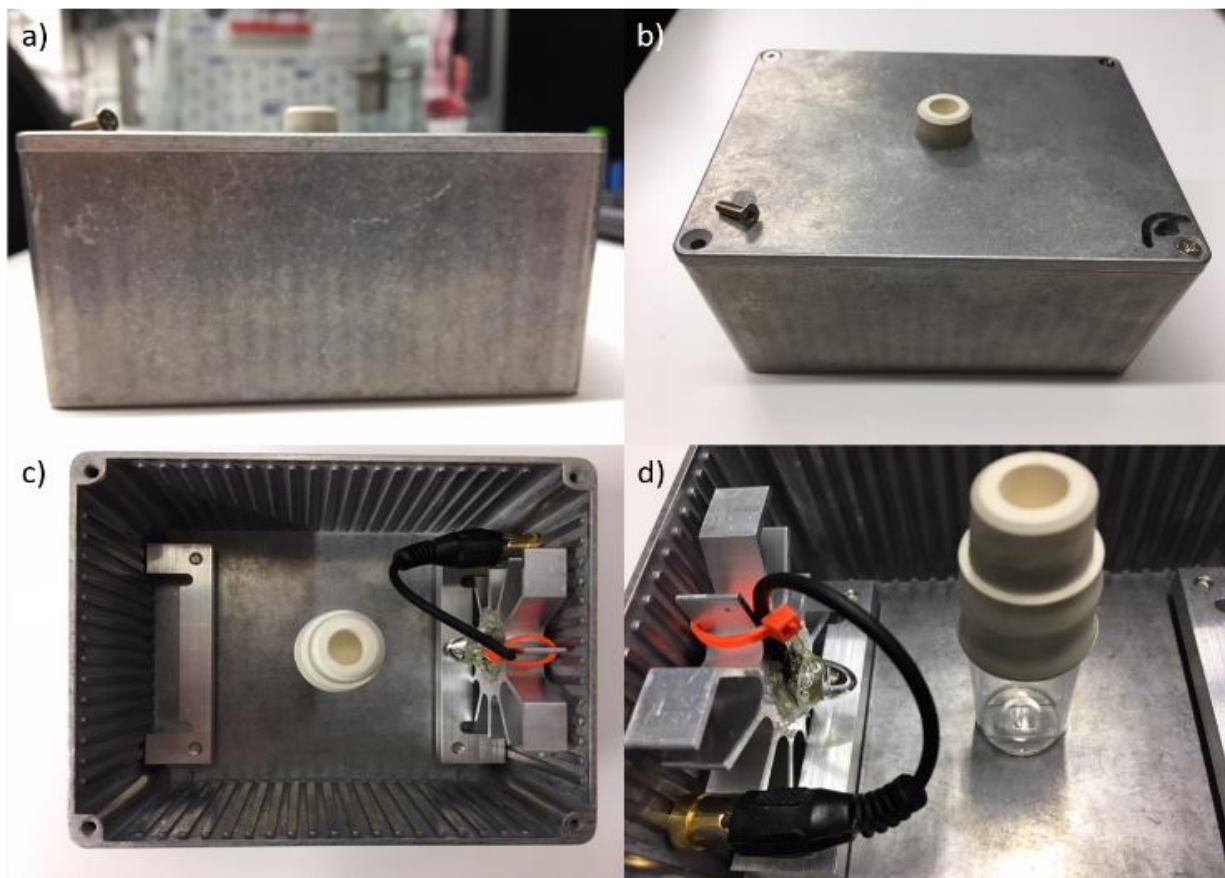


Catalyst	3 ^[a]	4 ^[a]	5 ^[a]	Yield [%] ^[b]
-	-	-	-	-
DMAP ($\lambda = 365$ nm)	1	4.5	1.5	82
DMAP ($\lambda = 448$ nm)	1	4	1	73
Fred_1	2	1	1	61
Fred_1 ($\lambda = 365$ nm)	1	4	3	61

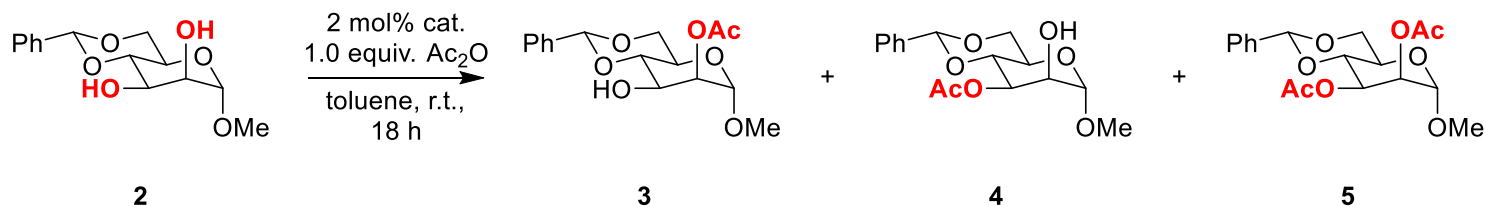
^[a]Ratio was determined *via* ^1H NMR ^[b]Yield was determined *via* ^1H NMR



^1H NMR in $\text{MeOH-}d_4$

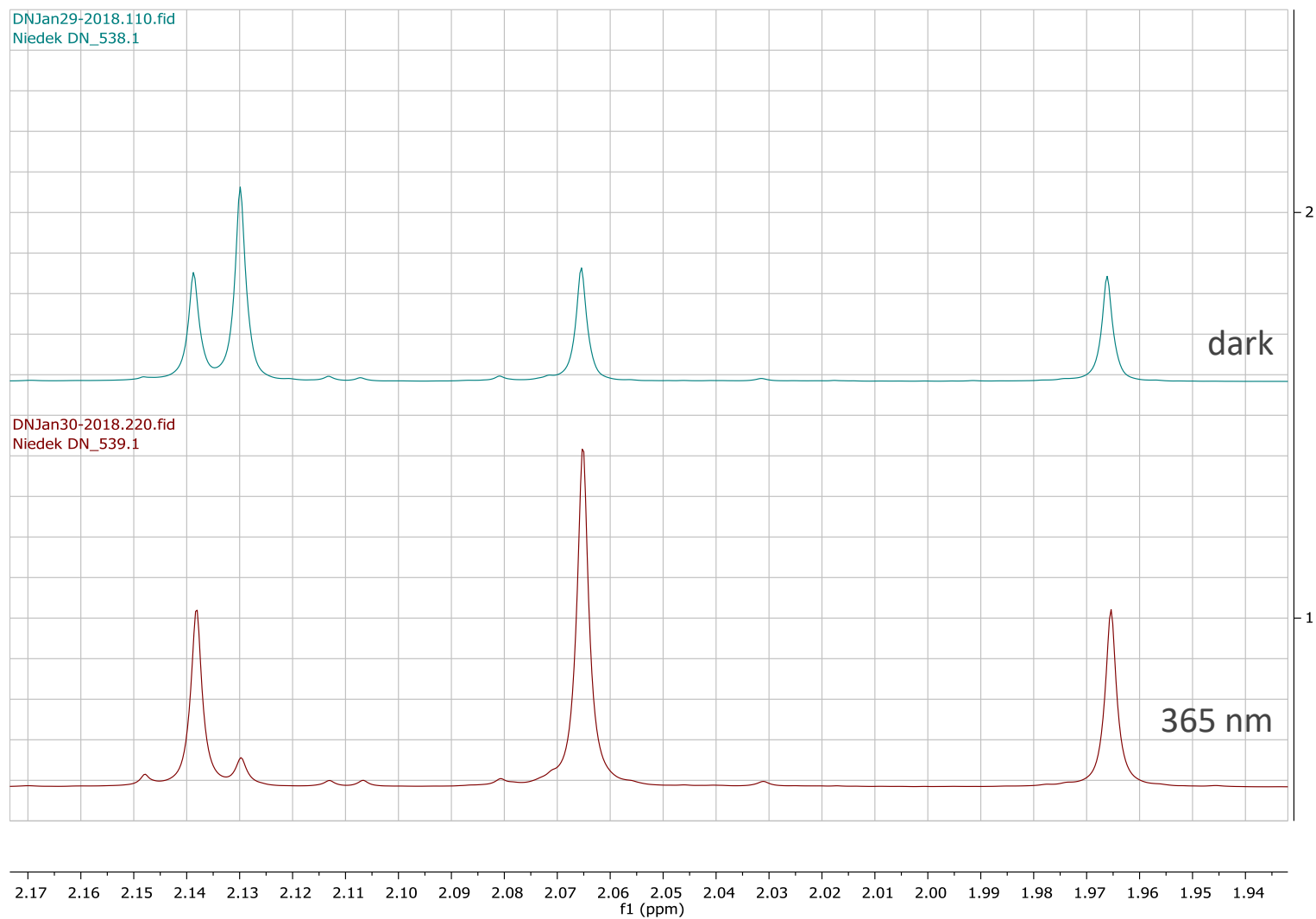


a) closed lightproof catalysis device b) reaction vessel equipped with septum to inject reactants and reagents c) inlet of the catalysis device with support for the LED and d) close-up view of the LED reaction vessel area



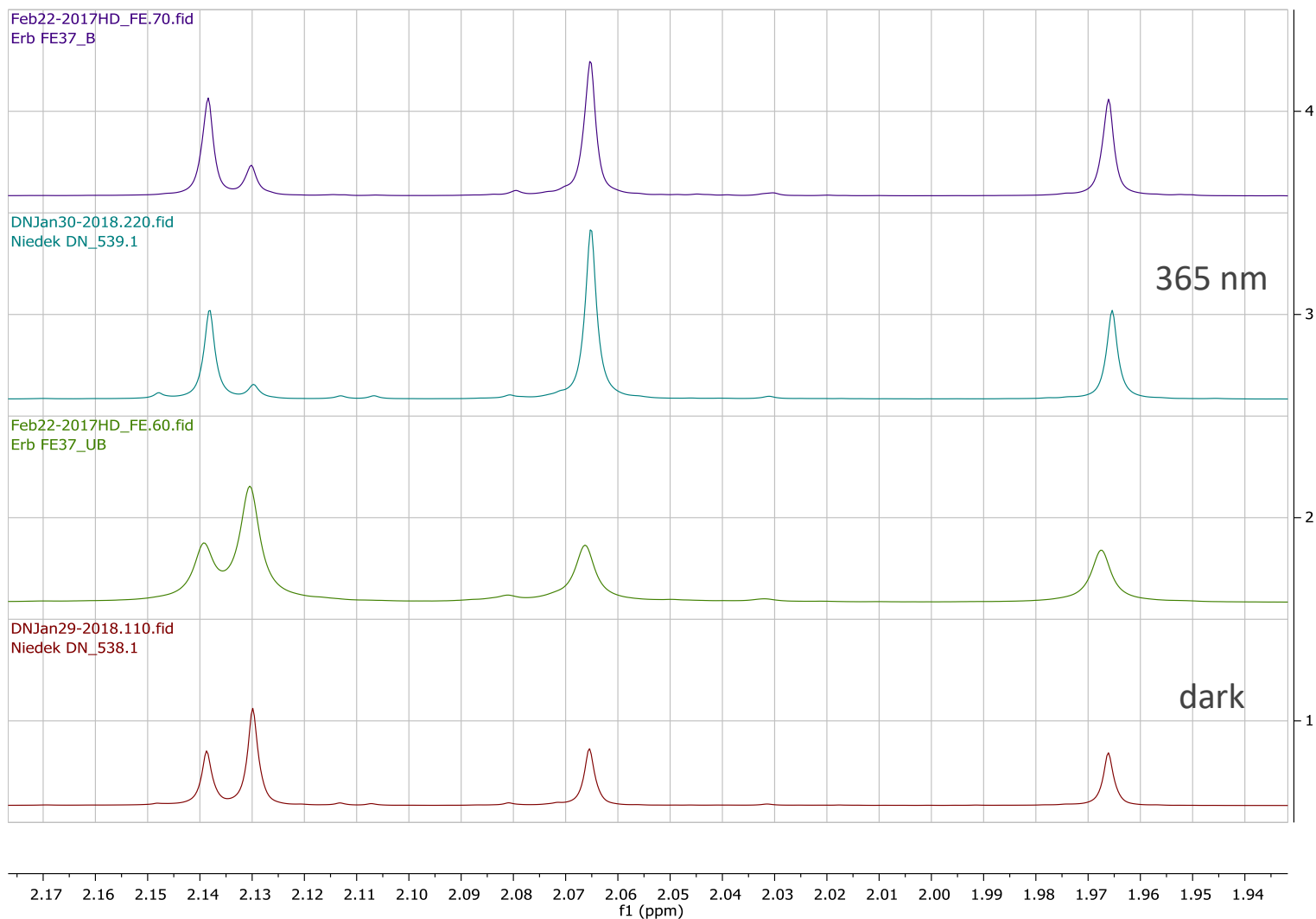
Catalyst	3 ^[a]	4 ^[a]	5 ^[a]	Yield [%] ^[b]
-	-	-	-	-
DMAP (λ = 365 nm)	1	4.5	1.5	82
DMAP (λ = 448 nm)	1	4	1	73
Fred_1	2	1	1	65
Fred_1 (λ = 365 nm) [cooled]	1	14	7	74

^[a]Ratio was determined *via* ¹H NMR ^[b]Yield was determined *via* ¹H NMR

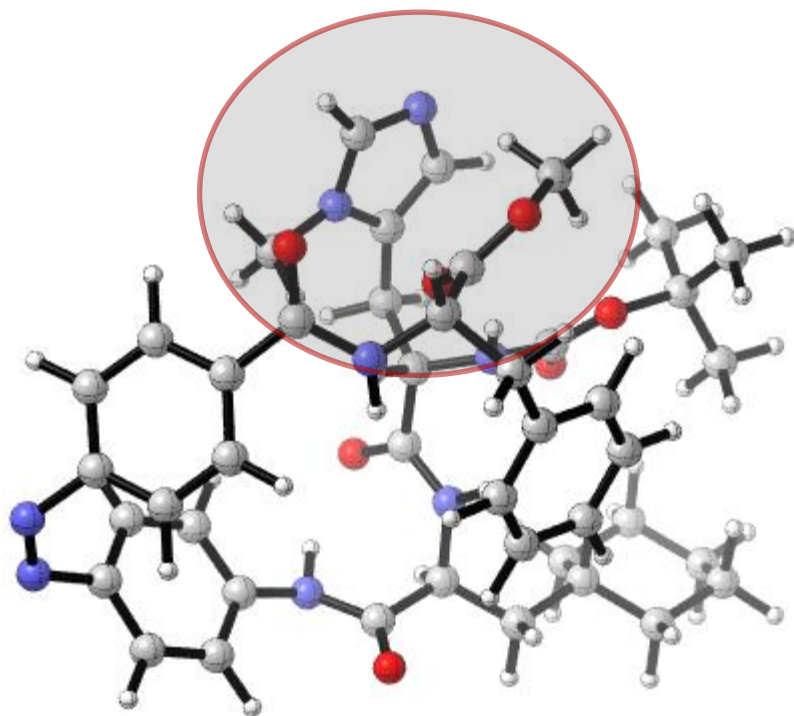


^1H NMR in $\text{MeOH-}d_4$

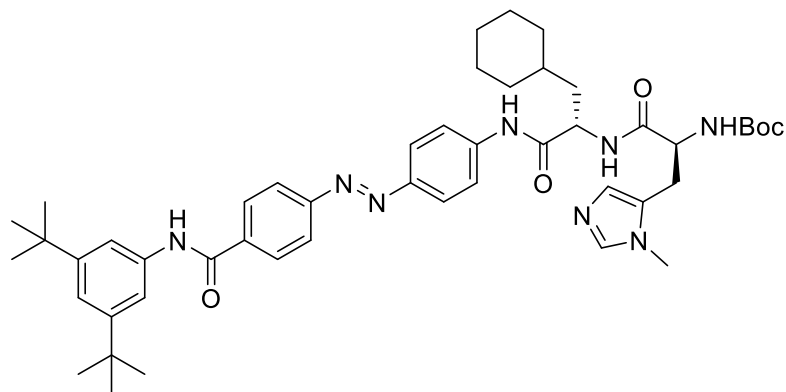
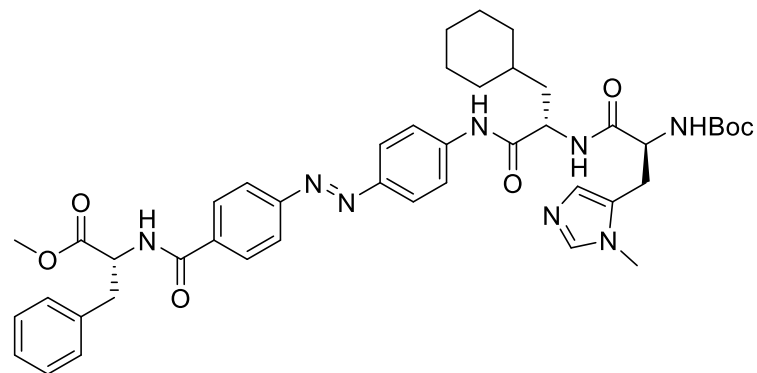
Results 4,6-*O*-benzylidene- α -D-mannopyranoside (old vs. new)



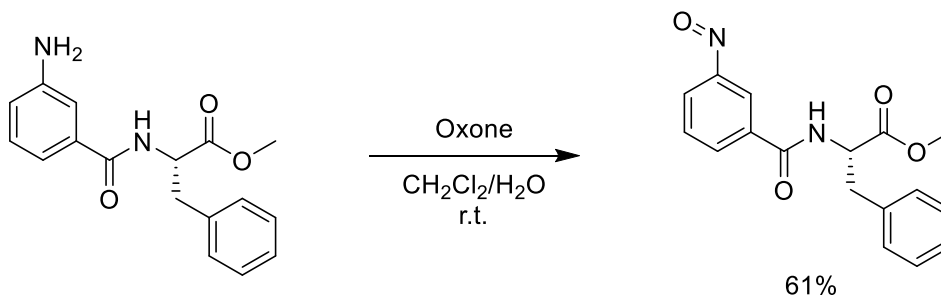
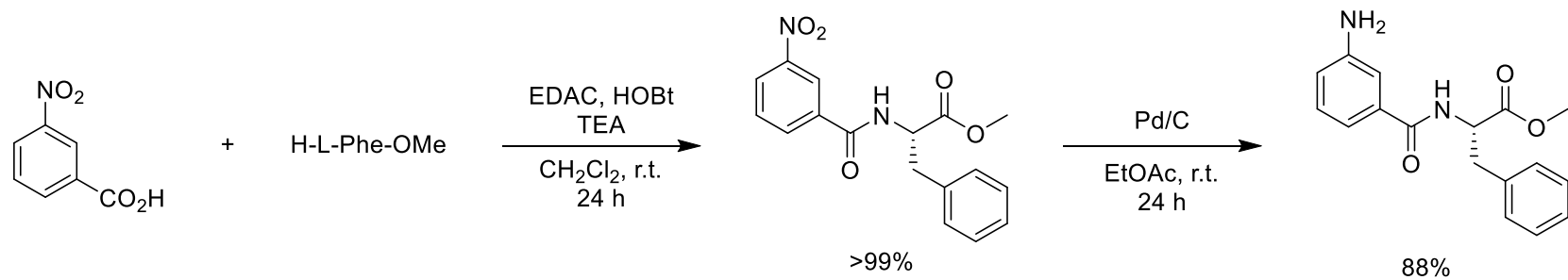
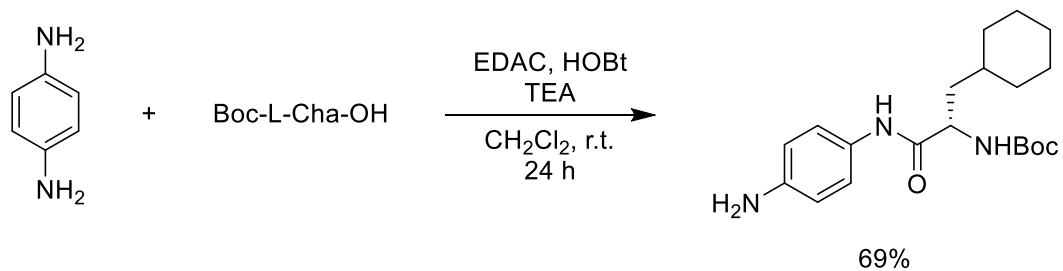
^1H NMR in $\text{MeOH-}d_4$

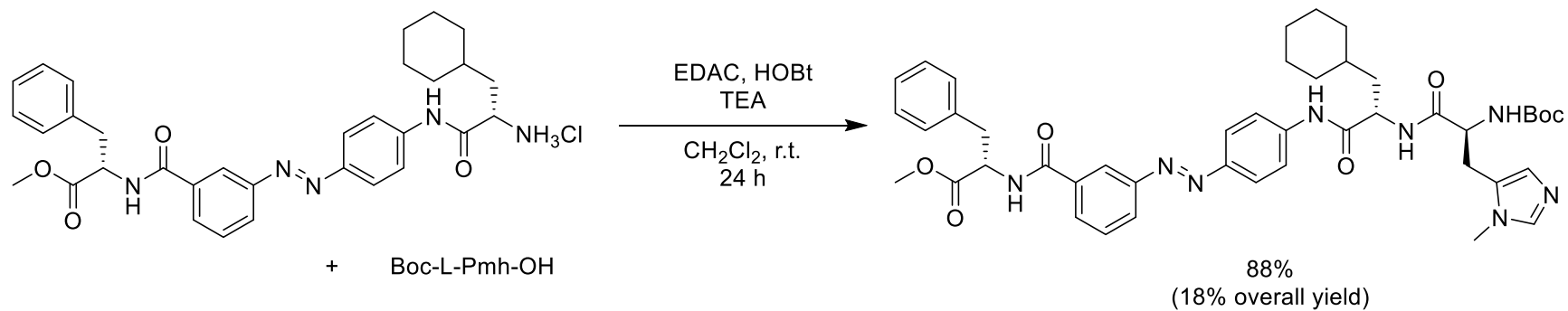
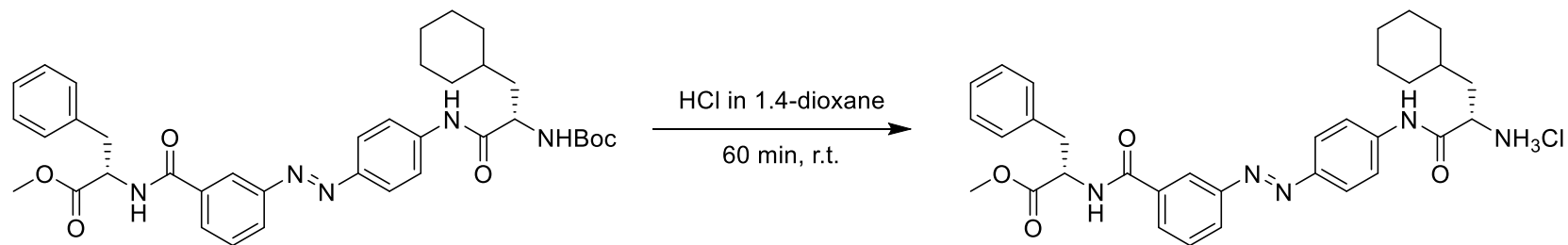
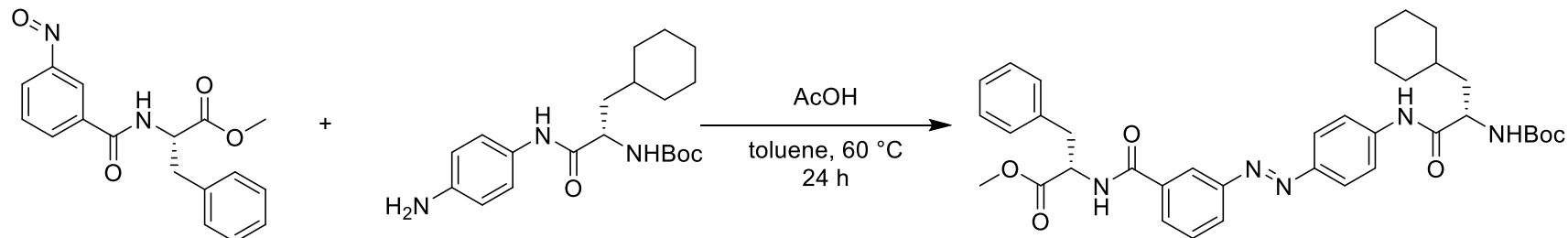


- L-Phe-OMe vs. D-Phe-OMe
- L-Phe-OMe vs. L-Phe-OBn
- L-Phe: ester vs. amide
- *ortho/ortho* vs. *ortho/meta*
- enantiomer of Fred_1

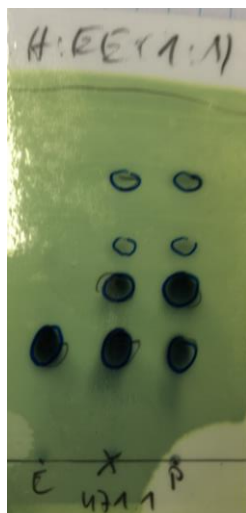
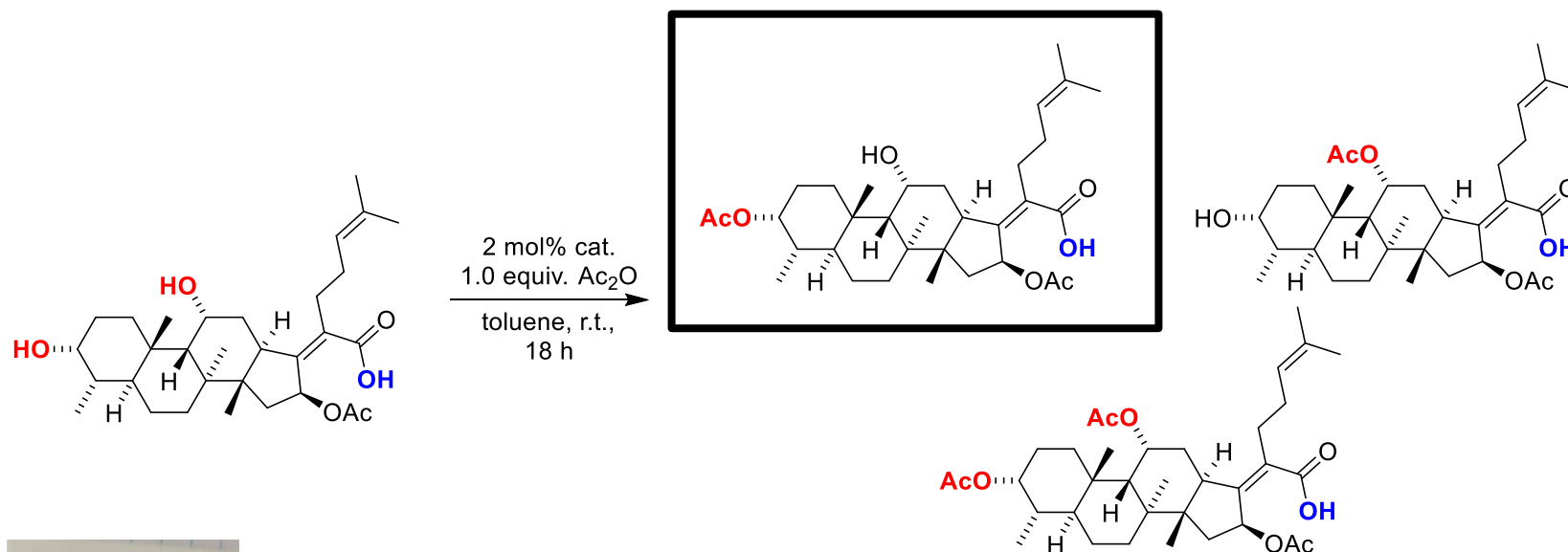


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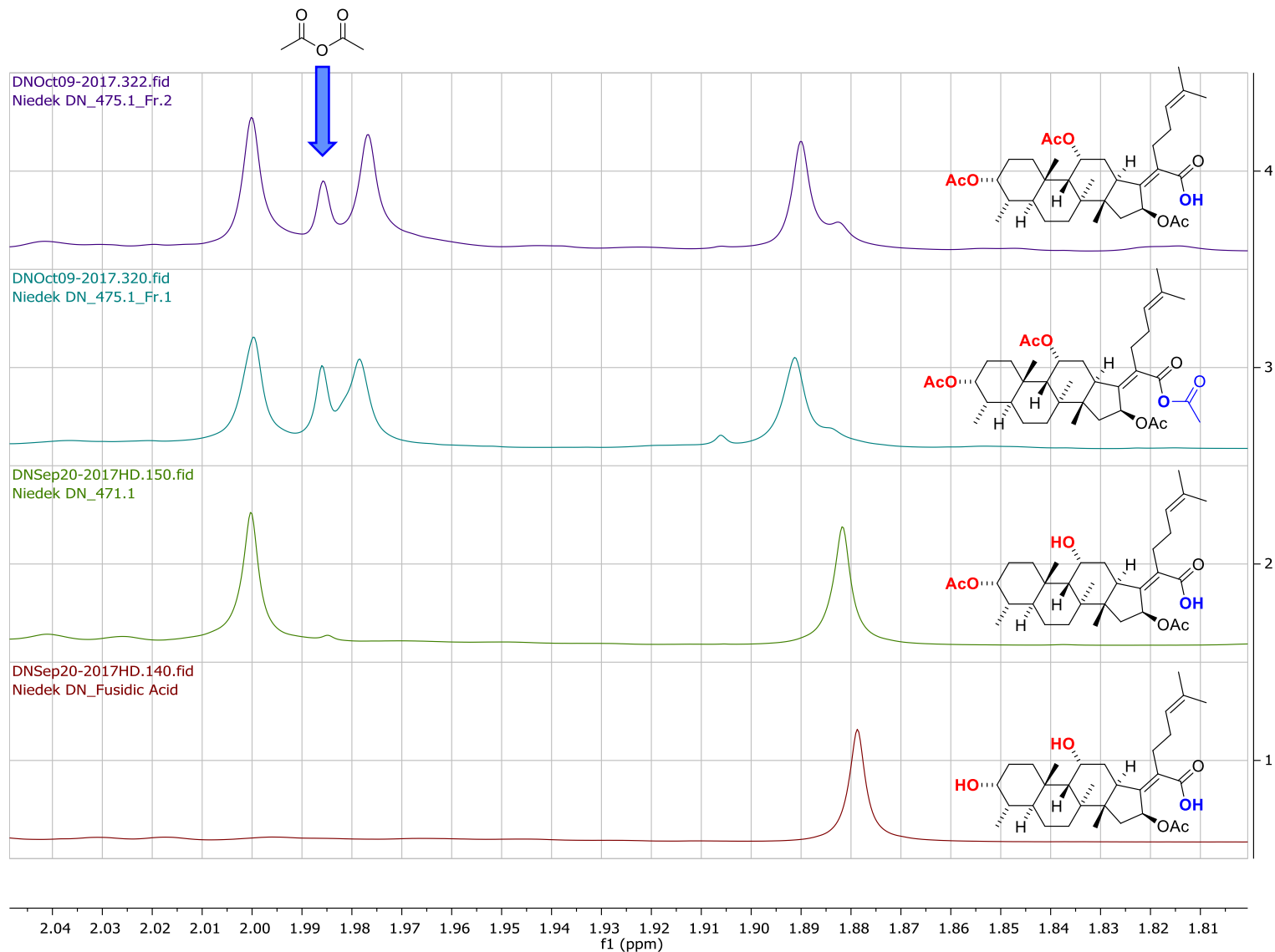


Regioselective Acylation of Fusidic Acid (Steroid Antibiotic)



← diacylated + anhydride
 ← diacylated
 ← monoacylated
 ← starting material

Regioselective Acylation of Fusidic Acid (Steroid Antibiotic)



C. K. Hill, J. F. Hartwig, *Nat. Chem.* **2017**, advance online publication.
(Functionalization of fusidic acid methyl ester)

Regioselective Acylation of Fusidic Acid (Steroid Antibiotic)

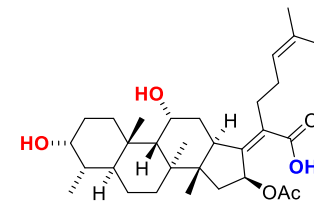
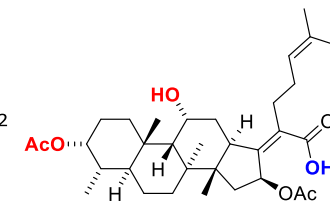
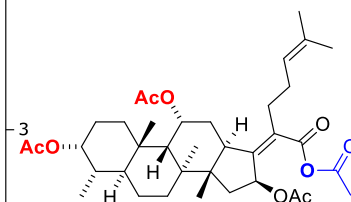
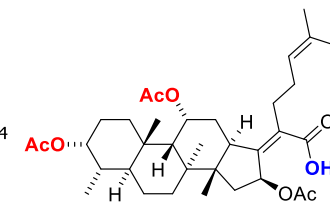
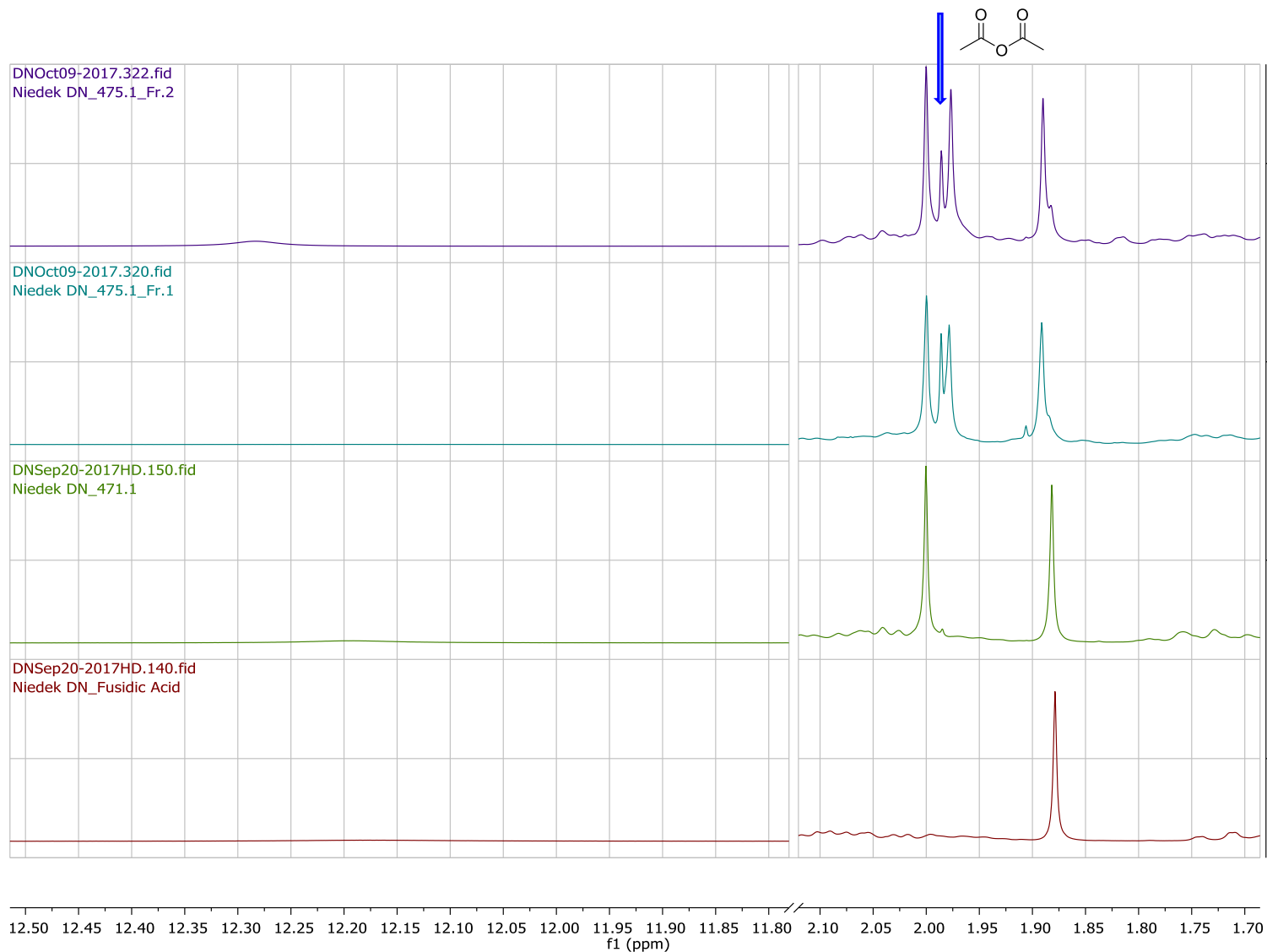


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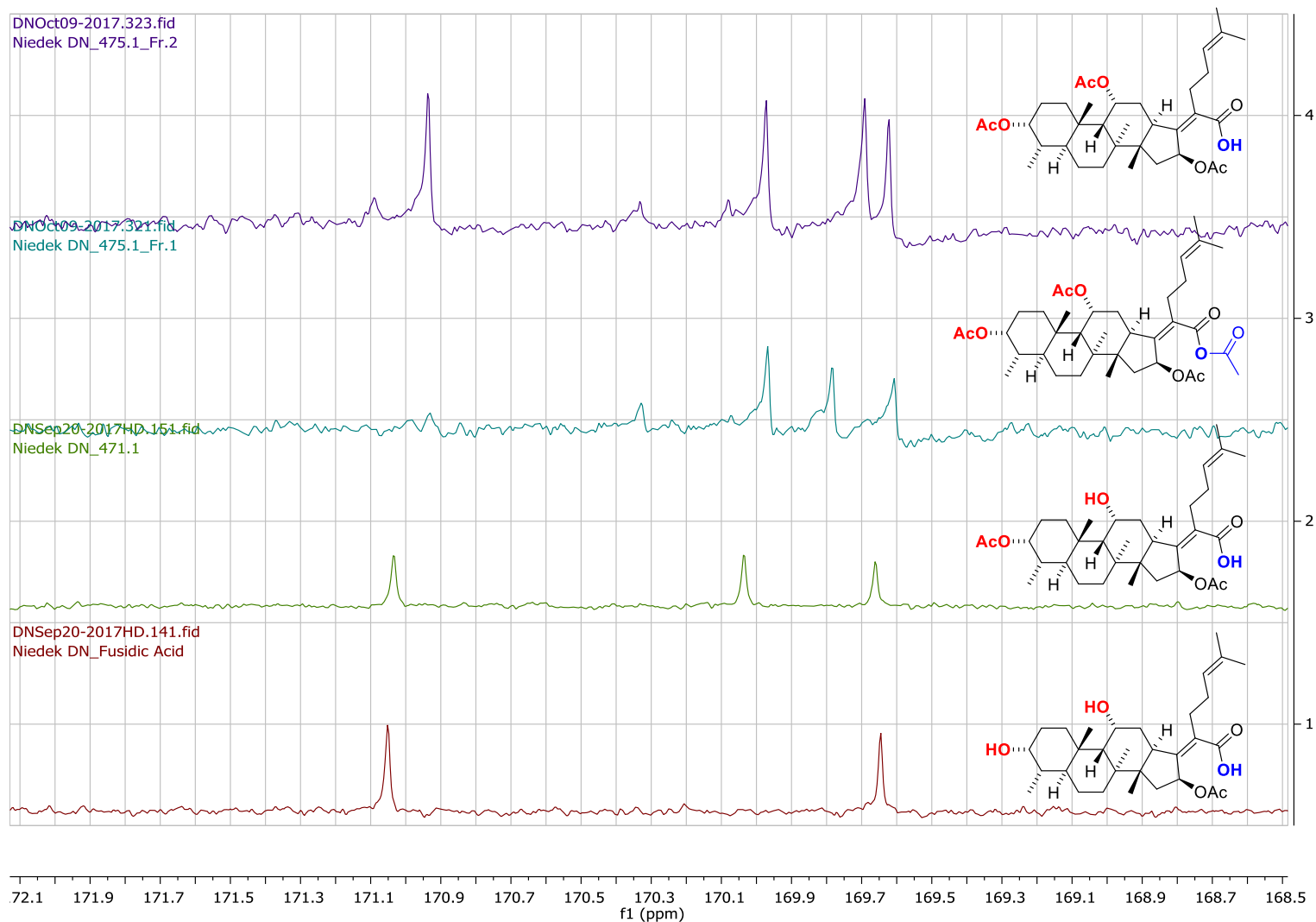
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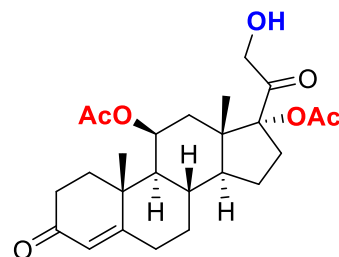
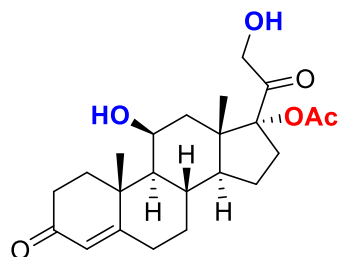
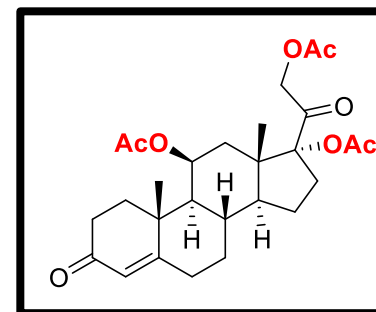
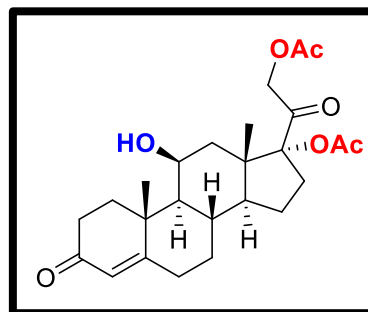
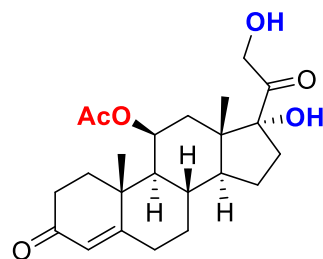
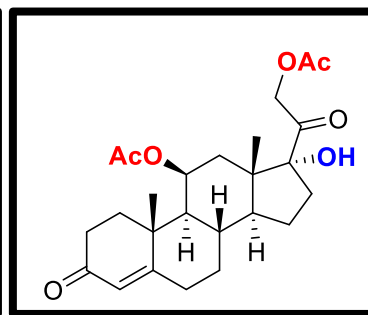
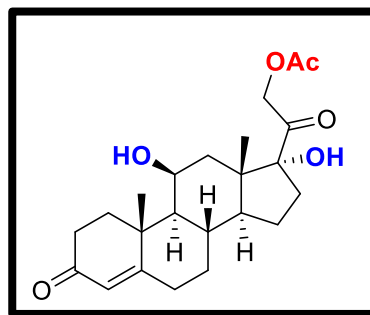
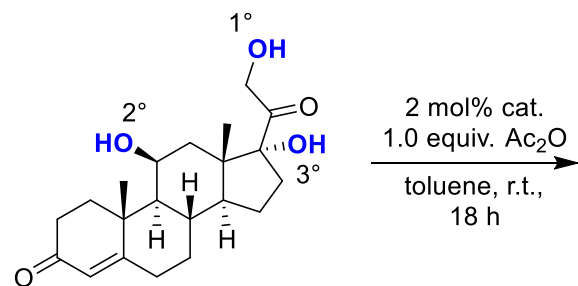


C. K. Hill, J. F. Hartwig, *Nat. Chem.* **2017**, advance online publication.
(Functionalization of fusidic acid methyl ester)

Regioselective Acylation of Fusidic Acid (Steroid Antibiotic)



C. K. Hill, J. F. Hartwig, *Nat. Chem.* **2017**, advance online publication.
(Functionalization of fusidic acid methyl ester)





- Development of a new concept controlling regioselectivity
- Preparation of peptide based catalysts
- Spectroscopic investigation of the new catalysts
- Design of a catalysis device
- Construction of the catalysis device
- Proof of concept using 4,6-*O*-benzylidene- α -D-mannopyranoside as a benchmark substrate



- Using the new catalysts for the acylation of 4,6-*O*-benzylidene- α -D-mannopyranoside
- Investigation of the efficiency of the new catalysts using fusidic acid and cortisol as further substrates
- UV/Vis characterization of all catalysts
- Determination of the *trans/cis* ratios in photostationary state (NMR, Ruth Gschwind)
- Find further potential reactions to expand the concept



- Prof. Dr. Peter R. Schreiner
- JPB, Eschi and Jan
- Alex, Raffi, Markus and Freddy
- Dr. Heike Hausmann, Steffen Wagner, Stefan and Anika Bernhardt
- PRS-Group





Thank you for your attention!

