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Z-Selective Fluoroalkenylation of (Hetero)Aromatic Systems by Iodonium Reagents in Palladium-Catalyzed Directed C–H Activation

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Abstract: The direct and catalytic incorporation of fluorine containing molecular motifs into organic compounds resulting high-value added chemicals represents a rapidly evolving part of synthetic methodologies, thus this area is in the focus of pharmaceutical and agrochemical research. Herein we report a stereoselective procedure for direct fluorovinylation of aromatic and heteroaromatic scaffolds. This methodology development has been realized by palladium-catalyzed *ortho* C–H activation reaction of aniline derivatives featuring the regioselectivity via directing groups such as secondary of tertiary amides, ureas or ketones. The application of non-symmetrical aryl(fluoroalkenyl)-iodonium salts as fluoroalkenylating agents allowed mild reaction conditions in general for this transformation. The scope and limitations have been thoroughly investigated and the feasibility has been demonstrated by more than 50 examples.

Keywords: C–H activation; Fluoroalkenylation; Heterocycles; Hypervalent compounds; Palladium

Introduction

The fluorine-containing functional groups have great impact on medicinal and agrochemical industry.[1] The replacement of hydrogen atoms with fluorine enables the fine-tune of certain properties of the molecules, such as conformation, pharmacological behaviour, metabolic stability, membrane permeability or lipophilicity through electronic and steric effects.[2] These principles in drug design allow to use fluorinated motifs as potential bioisosteres. Thus, fluoro- and trifluoromethyl alkenes mimic an ester or amide, and *gem*-difluoroolefins can act as a carbonyl moiety,[3] which have been exploited in different valuable chemicals with enhanced biological activity such as e.g. Tezacitabine, Trifluridine and Seletracetam (Figure 1). These fluorous molecular motifs could even offer an alternative to the prenyl group, which are exploited in pyrethroid insecticides (e.g. Tefluthrin, see Figure 1).

Since the number of FDA approved fluorine-containing drugs is increasing,[3b] there is a growing need to develop new methodologies for fluorine incorporation. Therefore, the versatile fluorinated alkene structural motifs are having an expanding attention (for instance hydrofluoroolefins as starting materials), which can lead also to the discovery of new reactivity for organic chemical applications.[4] In spite of its underrepresented biological and chemical applications, the fluoroalkenyl structural units, especially

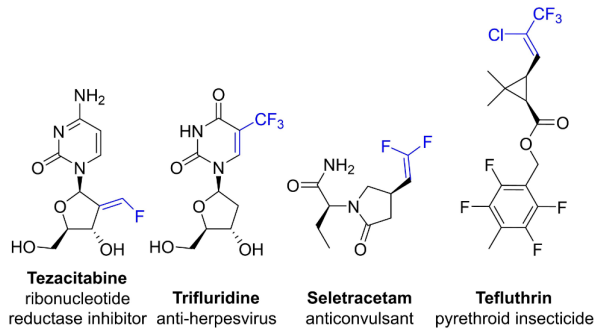
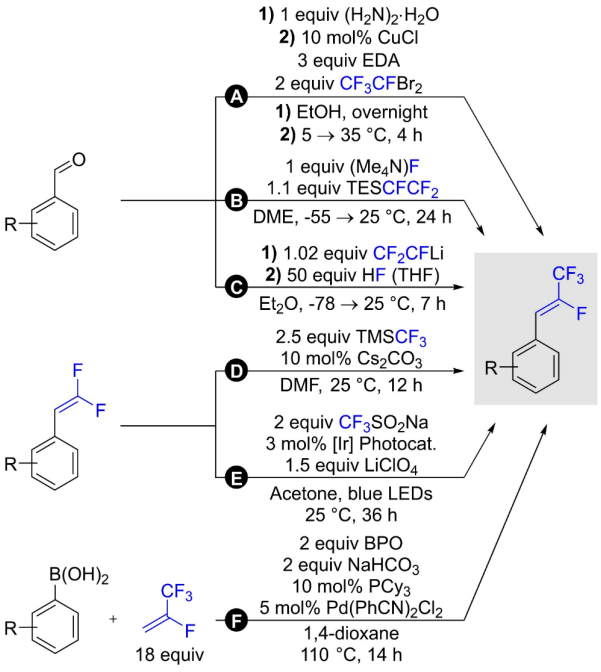


Figure 1. Fluoroalkenyl moieties in pharmaceutically and agrochemically active molecules.

2,3,3,3-tetrafluoroprop-1-en-1-yl functional group may serve as a key structural element of a diversified target-oriented synthesis.

The construction of tetrafluoropropenyl arenes was achieved by several pathways such as transformation of *in situ* generated hydrazones from aromatic aldehydes and ketones using copper catalyst and bases via carbene intermediate (Scheme 1A);[5] or combining aldehydes with the corresponding organometallic fluorovinyl reagent (such as silyl,[6] Scheme 1B or lithium organic compounds,[7] Scheme 1C) and the desired product can be obtained by the addition of fluoride anion (with vinylstannanes)[8] or by a terminal elimination step (using strong bases).[9] The geminal halogenated olefins are able to undergo a dehalogenative trifluoromethylation reaction using copper reagents.[10] Similarly to this, there are alternative approaches for straightforward trifluoromethylation reactions starting from *gem*-difluorostyrenes using trimethylsilyl-trifluoromethane ($TMSCF_3$) reagent (Scheme 1D)[11] or merging Langlois' salt (sodium triflinate) with iridium photoredox catalysis (Scheme 1. E).[12] The aromatic tetrafluoroalkenes are also accessible by palladium catalyzed oxidative Heck-type coupling of arylboronic acids and large excess of 2,3,3,3-tetra-fluoroprop-1-ene at 110 °C (HFO-1234yf,[4b] Scheme 1F).[13]



Scheme 1. Previous procedures for the introduction of tetrafluoropropenyl functional group into aromatic systems.

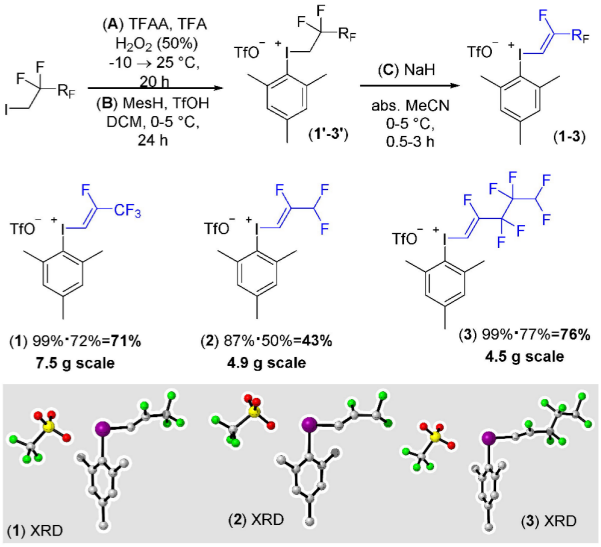
We envisioned a simple catalytic transformation, which allows the direct fluoroalkenylation of the aromatic systems with high selectivity under mild reaction conditions. Principally, the introduction of a directing group (DG) into an aromatic core opens the possibility to achieve an *ortho*-selective C–H activation possessing the practicability of a late-stage functionalization.[14]

The electrophilic iodonium reagents can act as outstanding partners in palladium-catalyzed directed C–H activation reactions,[15] and some of their representative gained application in direct fluoroalkylations.[16] Considering the opportunities offered by fluoralkyliodonium species, we turned our attention to aryl(fluoroalkenyl)iodonium salts, which were first discovered by Umemoto and Gotoh.[17] We anticipated that the hypervalent iodine fluoroalkenylation reagents in combination with palladium-catalyzed C–H activation will grant mild and efficient functionalization, and we aimed to develop a regioselective C–H tetrafluoropropenylation reaction of aromatic and heteroaromatic systems.

Results and Discussion

To start our investigation, we synthesized three different (fluoroalkenyl)mesityliodonium salts (**1-3**) starting from commercially available fluoroalkyl iodides (Scheme 2). After the first oxidation step of the synthesis, a consecutive aromatic substitution takes place and generate (fluoroalkyl) mesityliodonium salts **1'–3'** from mesitylene in the presence of TfOH. After the isolation of the fluoroalkyliodonium salts **1'–3'**, the HF elimination reaction was performed using NaH and the key fluoroalkenyl reagents (**1–3**) were obtained in 43–76% combined yield for two steps, up to 7.5-gram scale.

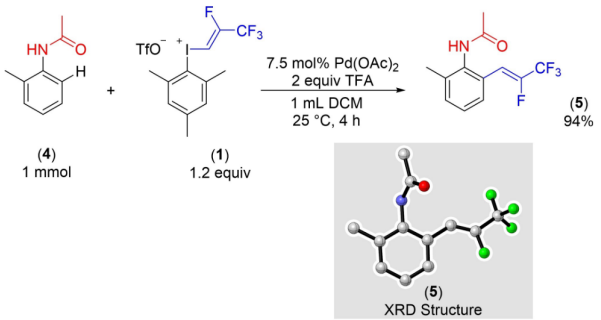
After the synthesis of the iodonium reagents we checked the applicability of the mesityl-(tetrafluoropropenyl)iodonium triflate (**1**) in palladium catalyzed *ortho* C–H activation reaction of 2-methylacetanilide (**4**) with the modification of some reaction parameters including the amount of acid, solvent and reaction



[a] Reaction stoichiometry: A: 5 mmol fluoroalkyliodide, 7.2 equiv TFAA, 0.1 equiv TFA, 1.7 equiv H_2O_2 (50% aq.) B: 1.55 equiv Mesytilene (Mes-H), 1 equiv TfOH; C: 1.1 equiv NaH

Scheme 2. Synthesis of fluoroalkenyl-(mesityl)iodonium salts.[18]

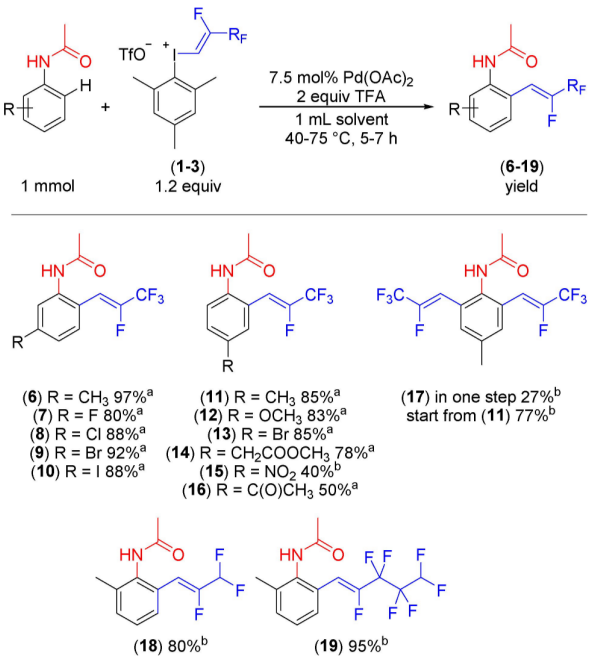
conditions we found that the reaction works perfectly under the previously developed conditions (for further details see SI).[15c,d] Under the optimal reaction conditions, in the presence of 7.5 mol% of palladium(II) acetate catalyst, 2 equivalents of trifluoroacetic acid (TFA) and dichloromethane (DCM) as solvent, we performed the tetrafluoropropenylation reaction of 2-methylacetanilide (**4**) with iodonium salt **1** at 25 °C in 4 hours took place, and we successfully isolated the desired 2,3,3,3-tetrafluoropropenylated product (**5**) selectively with Z double bond geometry (Scheme 3). The structure and the orientation were confirmed by XRD measurements.



Scheme 3. Optimization of aryl(tetrafluoro-propenyl)iodonium salts in C–H activation reaction of 2-methylacetanilide.

After the demonstration of the applicability of tetrafluoropropenyl-mesityliodonium salt in palladium-catalyzed C–H activation reaction we investigated the scope and limitations of *Z*-selective fluoroalkenylation of aromatic compounds bearing different directing groups with mesityliodonium salts bearing various fluoroalkenyl groups.

First, we converted a wide variety of *meta*- and *para*-substituted acetanilides into analogous tetra-fluoropropenyl derivatives (Scheme 4). We found that the 3-methylacetanilide reacted smoothly at 40 °C providing **6** in 97% of yield. The halogenated acetanilide derivatives simply underwent this reaction and gave compounds **7**, **8**, **9** and **10** in very good to excellent yields. There was no significant difference between the electron donating methyl- or methoxy groups and bromide functionalities on the aryl ring, as these substrates were functionalized quickly and the appropriate products **11**, **12** and **13** were isolated in 83–85% yield range. Product **14** having methylene-carboxylic ester function on the aromatic ring of the anilide was obtained in 78% yield. More electron-deficient aromatic systems such as nitro- (**15**) or acylanilides (**16**) resulted lower, 40% and 50% yields even at elevated temperature. Through an example of **17**, we have demonstrated the possibility of a twofold C–H activation and fluoroolefination reaction. Carrying out

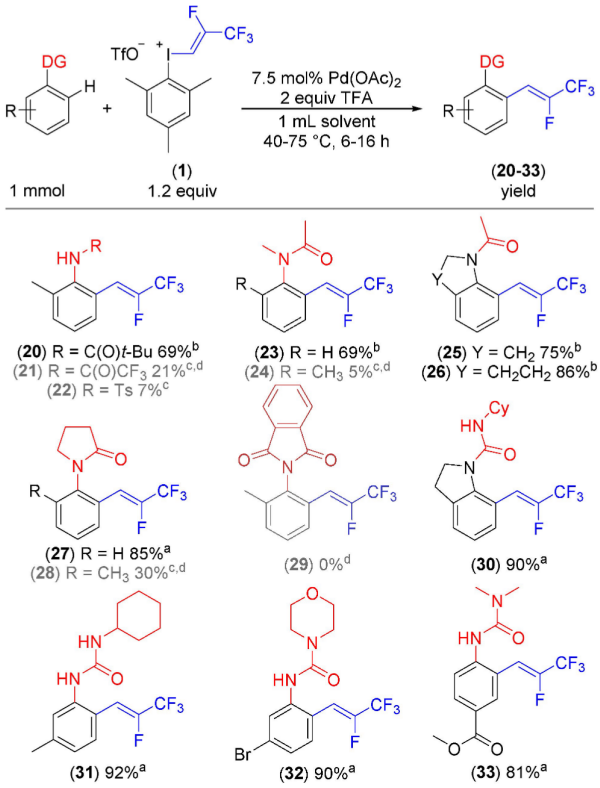


[a] 1 mL DCM solvent, 40 °C, 5-7 h.
[b] 1 mL 1,2-DCE solvent, 75 °C, 6-7 h.
[c] 0.05 mmol scale, 0.5 mL 1,2-DCE solvent, 75 °C, 24 h.

Scheme 4. *Z*-selective 2,3,3,3-tetrafluoropropenylation of aromatic acetamides by Pd-catalyzed C–H activation.

the reaction with a single loading (2.4 equivalents) of iodonium salt **1** the reaction resulted 27%, while in a sequential tetrafluoro-alkylation approach the *bis*-product formed in 77% yield. Additionally, different 2° and 3° amide functional groups were tested as DGs in this regioselective palladium-catalyzed C–H activation reaction (Scheme 5). By exchanging the DG to the bulkier pivalamide, the desired functionalization of 2-metylpivalanilide was achievable with full conversion only at 75 °C and **20** was obtained in 69% yield, compared to product **5** which was isolated in 94% yield.

The transformation was extended with the (*Z*)-trifluoropropenylation of 2-methylacetanilide (**4**) using iodonium salt **2**, and the reaction provided the corresponding product **18** in 80% of yield. Since **2** showed decreased reactivity due to the so-called *ortho* effect,[19] in order to reach full conversion, the application of forcing conditions (75 °C, 6 h and 1,2-DCE) was necessary. Similarly, the (*Z*)-heptafluoropentenylation reaction with **3** at elevated temperature produced the product **19** in excellent, 95% of yield.



[a] 1 mL DCM solvent, 40 °C, 6-7 h.
[b] 1 mL 1,2-DCE solvent, 75 °C, 6-16 h.
[c] 0.05 mmol scale, 0.5 mL 1,2-DCE solvent, 75 °C, 24 h.
[d] Conversion was determined by GC-MS measurement (for details, please see Supporting Information).

Scheme 5. *Z*-selective 2,3,3,3-tetrafluoropropenylation of aromatic ureas and secondary and tertiary amides by Pd-catalyzed C–H activation.

Due to the electron-deficient nature of trifluoroacetamide and tosylamide groups in the arene, these DGs were not sufficient for an effective coordination of Pd catalyst, thus these substrates were not suitable for the direct C–H activation. The desired products **21** and **22** were formed only with 21% an 7% conversion.

We found that the elevated temperature is required for the functionalization of tertiary amides, and the tetrafluoropropenyl moiety was introduced into the aromatic core of *N*-methylacetanilde yielding **23** in 69%. In contrast with this, the presence of an *ortho*-methyl group of the arene blocked this reactivity and only traces of **24** (5% of conversion by GCMS) were determined. Since the electronic properties do not change dramatically, we can conclude the unfavourable influence of steric reasons occurring between the DG and *ortho*-methyl.

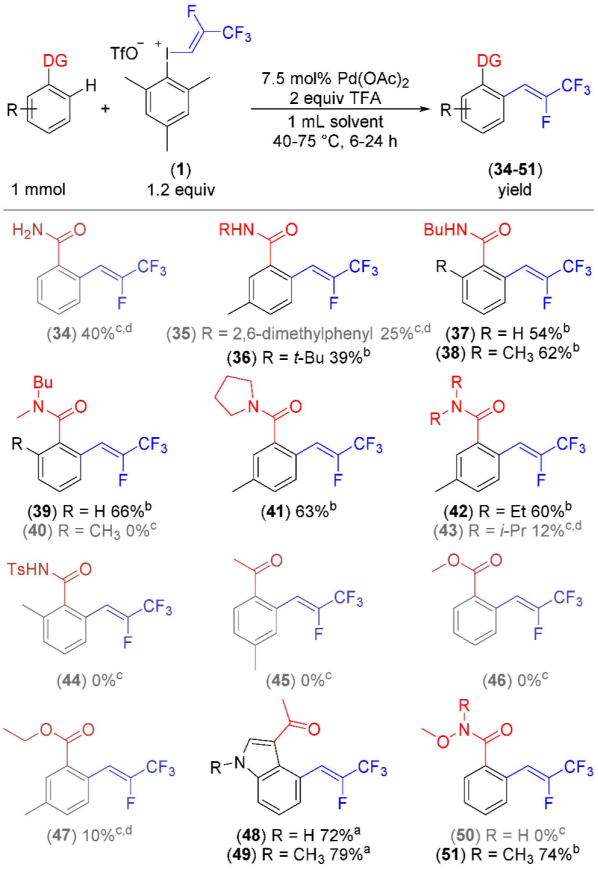
Repeating the experiment with cyclic derivatives bearing a bridge between the aryl ring and the DG afforded better yields under similar reaction conditions and the 5-membered **25** isolated with 75% and the 6-membered cyclic tertiary amide **26** obtained with very good, 86% yield. However, *N*-phenyl-pyrrolidine-2-one proceeded easily and gave 85% yield of **27**, which is allowed solely the mono-selective C–H activation and the tetrafluoropropenylation (as well as in case of **23**).

Remarkably, the *ortho*-methyl group hindered the reaction and in case of **28** only 30% of conversion was available even under forcing conditions.

The design of bulky imide DG has no advantage in C–H activation, taking into consideration the steric reasons. Expectedly, due to the presence of *ortho*-methyl group and large DG, the formation of **29** is disadvantageous.

Besides the amides, the aromatic ureas also have been subjected to the *Z*-selective *ortho*-tetrafluoropropenylation procedure. We studied the tolerance of DGs as well as the substitution pattern. As a result, we concluded that the urea functional group albeit it decomposes more easily, contributes to the electron-rich character of arene and for this reason is perfectly useable in directed C–H bond activation reaction. In this regard, cyclic, *meta*-methyl, *meta*-bromo and *para*-ester urea derivatives (**30**–**33**) were isolated in very good to excellent yields (81–92%).

In order to immerse in the synthetic performance of our *Z*-selective, palladium-catalyzed C–H activation methodology, we extended the scope to benzamides, aromatic esters and ketones (Scheme 6). Already at the beginning we had to conclude that the tetrafluoropropenylation may also reaches the limit such as in case of primary amides. The formation of unidentifiable side-products was observed by TLC analysis in



[a] 1 mL DCM solvent, 40 °C, 24 h.
[b] 1 mL 1,2-DCE solvent, 75 °C, 6 h.
[c] 0.05 mmol scale, 0.5 mL 1,2-DCE solvent, 75 °C, 24 h.
[d] Conversion was determined by GCMS measurement.

Scheme 6. *Z*-selective 2,3,3,3-tetrafluoropropenylation of benzamides and ketones by Pd-catalyzed C–H activation.

this case, and the conversion of **34** remained as low as 40% even at 75 °C. Similarly, *N*-(2,6-dimethylphenyl)-benzamide transformed to **35** only in 25% conversion. In contrast, we were able to synthesize the *N*-(*tert*-butyl)benzamide derivative **36** in 39% yield, and the *n*-butyl substituted benzamide substrates gave products **37** and **38** in 54% and 62% yield, respectively.

Continuing the experimentation with tertiary benzamides, we found that the reaction mixture contained less component and the unfavourable side-reactions are completely supressed. This is closely connected to the protection of the nucleophilic NH of benzamides, although the substrates with bulkier DGs became more sensitive from steric aspects.

In this way, we tested *N*-butyl-*N*-methylbenzamides, which provides the *N*-methylated analogues of **37** and **38**. Notably, the yield of **39** increased and reached a better 66%, but the incorporation of a methyl group into the *ortho* position of the aryl ring of **40** absolutely stopped the reaction. In this scenario the cyclic amide **41** and the *N*,*N*-diethyl compound **42** (starting from *N*,*N*-diethyl-3-methylbenzamide, DEET) were isolated in 63% and 60% of yield. However, in this series the *N*,*N*-diisopropylbenzamide was not efficiently transformed, and only 12% of conversion was reachable (**43**).

Decreasing the electron density on the DG and the aromatic core is leading to unsuccessful synthetic attempts. This trend can be observed in case of *N*-tosylated benzamide **44**, and correspondingly by acetophenones (such as **45**) or benzoates (**46**, **47**). Nevertheless, the more electron-rich aromatic ketones such as indoles were ready for the direct tetrafluoropropenylation in the *C4* position. The unprotected **48** and its *N*-methylated derivatives **49** ware isolated in 72–79% yields. Additionally, the synthetically useful Weinreb amide was found to be a suitable substrate for the C–H activation reaction as long as its nitrogen atom owned a methyl group, **51** was isolated in 74% yield.

Conclusion

In conclusion, the applicability of palladium-catalyzed C–H activation reaction of fluoroalkenyl-(mesityl) iodonium salts was shown in a simple and direct fluoroalkenylation reaction of aromatic and heteroaromatic compounds having various directing groups such as secondary and tertiary amides of anilides, ureas, benzamide derivatives or ketones. Under the applied mild reaction conditions the introduction of the fluoroalkenyl moieties took place with high stereoselectivity providing the desired fluoroalkenyl products exclusively with *Z*-double bond geometry. The electronic and steric effects on the coupling reaction were carefully studied including the substituents of arenes and directing groups responsible for the *ortho*-direction. As a result, we demonstrated that the transformation is successfully applicable on various substrates having versatile functional groups to provide novel fluoroalkenylated compounds. Thus, the developed direct fluoroalkenylation reaction could serve as a useful late-stage functionalization strategy for biology and medicinal chemistry applications.

Experimental Section

(*Z*)-Fluoroalkenylation of aromatic and heteroaromatic compounds: A 4 mL screw-cap vial was charged with *palladium (II) acetate catalyst* (0.075 mmol, 7.5 mol%, 16.8 mg), *aromatic compound* (1 mmol) and *fluoroalkenyl-(mesityl)iodonium salt* (1.2 mmol, 1.2 equiv.) and equipped with a magnetic stirring bar. Then 1 mL of *solvent* (dichloromethane or 1,2-dichloroethane) and *trifluoroacetic acid* (2 mmol, 2 equiv., 155 µL) then the vial was closed and the solution was stirred for 4–24 hours

at 25–75 °C. The reaction mixture turned from pale yellow to dark black. The solution was diluted with 25 mL ethyl acetate and extracted with 2 × 10 mL cc. $NaHCO_3$ solution, and 10 mL cc. NaCl solution. The organic phase solution was separated and dried on sicc. $MgSO_4$ then evaporated onto Celite. The crude product was purified by normal phase middle-pressure column chromatography using silica gel and hexane – ethyl acetate eluent. The fractions of the product were combined and the solvent was evaporated. The product was dried at 25 °C under high-vacuum.

The CCDC depository number of structures **1**, **2**, **3** and **5** are 2106966–2106969, respectively. CCDC-2106966-2106969 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

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