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Enantioselective NHC-Catalyzed Redox [2+2] Cycloadditions with Perfluoroketones: A Route to Fluorinated Oxetanes

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Abstract: The N-heterocyclic carbene (NHC) catalyzed redox formal [2+2] cycloaddition between α-aroyloxyaldehydes and perfluoroketones, followed by ring-opening in situ delivers a variety of perfluorinated β-hydroxycarbonyl compounds in good yield, and excellent diastereo- and enantioselectivity. Through a reductive work-up and subsequent cyclization, this protocol offers access to highly substituted fluorinated oxetanes in two steps and in high *ee*.

Organocatalysis has grown to become one of the most important sub-classes of organic chemistry, responsible for the development of a vast array of novel processes and catalytic modes.[1] Within this field, the use of N-heterocyclic carbenes (NHCs) has become popularized due to the variety of unusual catalytic intermediates that can be accessed from simple starting materials.[2] NHC-catalyzed redox processes can be used to generate a number of these useful catalytic intermediates, key among which is azolium enolates.[3] Mono-substituted azolium enolates can be accessed directly from starting materials such as α-haloaldehydes,[4] enals,[5] and *p*-nitrophenol esters.[6] Alternatively, Rovis and co-workers[7] and Chi and co-workers[8] have used aldehydes in conjunction with a stoichiometric oxidant to generate azolium enolates. Our previous work has shown the ability of bench-stable α-aroyloxyaldehydes to access azolium intermediates through an NHC-redox mechanism.[9] These studies and numerous others have shown the ability of azolium enolates to undergo a range of [4+2] cycloaddition reactions.[4–8] To date di-substituted azolium enolates derived from the reaction of NHCs with alkylarylketenes undergo [2+2] cycloadditions with aryl aldehydes and imines to form β-lactones and β-lactams respectively,[10] while [2+2] cycloadditions of mono-substituted azolium enolates have received little attention.[8,11] In this area, Chi and co-workers have reported two isolated examples of oxidative [2+2] cycloadditions between hydrocinnamaldehyde and trifluoroacetophenones, which requires superstoichiometric quantities of quinone as an oxidant (see Scheme 2a).[8]

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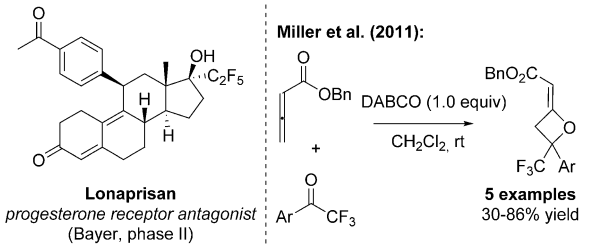
Perfluorinated heterocycles are of great industrial relevance, with a number of biologically active molecules, such as Lonaprisan (Bayer), currently under development containing such functionality (Scheme 1).[12] However, methods for the introduction of perfluorinated groups are currently limited,[13] and

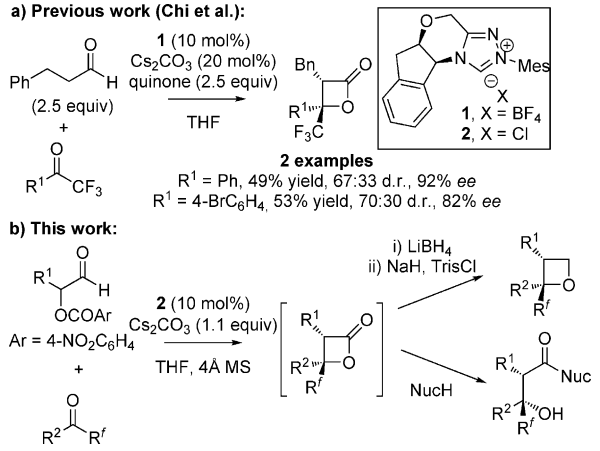


Scheme 1. Lonaprisan, a pentafluoroethyl-substituted progesterone receptor antagonist from Bayer,[12] and recent work on the synthesis of fluorinated oxetanes from the group of Miller.[18a]

these often consist of direct perfluorination, as opposed to utilizing perfluoro-containing building blocks such as ketones. Similarly, the oxetane motif has received considerable attention within medicinal chemistry due to the physicochemical properties it can impart onto molecules,[14] as well as its potential to be used as a bioisostere for the ketone functional group or a more lipophilic replacement for the *gem*-dimethyl moiety.[14] As such, novel approaches to oxetane scaffolds are of great interest, and in recent times a number of methods have been developed (Scheme 1).[15] Perfluorinated oxetanes have shown numerous applications in the literature, ranging from building blocks for inkjet polymers,[16] to inhibitors for numerous biological targets.[17] Despite this popularity, only limited studies on the synthesis of such compounds have been reported, often utilizing an allenoate [2+2] cycloaddition, as developed by Miller.[18a]

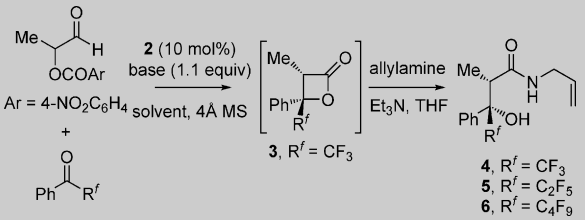
In this manuscript, the enantioselective NHC-catalyzed redox formal [2+2] cycloaddition between α-aroyloxyaldehydes and fluorinated ketones, followed by in situ ring-opening to form a variety of fluorinated quaternary β-hydroxycarbonyl compounds with excellent diastereo- and enantioselectivity is described. Through a reductive work-up and subsequent cyclization, this protocol allows access to highly functionalized stereodefined fluorinated oxetanes (Scheme 2b).

Initial studies into the NHC-catalyzed redox formal [2+2] cycloaddition investigated potential reaction conditions with perfluorinated ketones (Table 1). Consideration of both organic



Scheme 2. a) Oxidative NHC-catalyzed [2+2] cycloaddition from the group of Chi.[8] b) An asymmetric NHC-catalyzed formal [2+2] cycloaddition leading to fluorinated oxetanes.

Table 1. Formal [2+2] cycloaddition optimization.



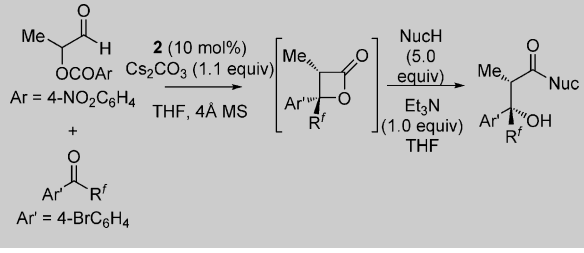
Entry	R_f	Solvent	Base	d.r.[a]	**3** NMR yield [%][b]	Amide yield [%][c]	Amide *ee* [%][d]
1	CF_3	THF	Et_3N	71:29	48	–	–
2	CF_3	THF	iPr_2NEt	70:30	50	–	–
3	CF_3	THF	Cs_2CO_3	73:27	88	–	–
4	CF_3	CH_2Cl_2	Cs_2CO_3	80:20	61	–	–
5	CF_3	Et_2O	Cs_2CO_3	72:28	58	–	–
6	CF_3	toluene	Cs_2CO_3	68:32	55	–	–
7	CF_3	THF	Cs_2CO_3	76:24	–	57	99
8	C_2F_5	THF	Cs_2CO_3	>95:5	–	74	96
9	C_4F_9	THF	Cs_2CO_3	>95:5	–	45	96

[a] d.r. determined by analysis of the crude ^{1}H NMR spectra. [b] Combined NMR yield of both diastereomers determined by analysis of the crude ^{1}H NMR spectra with reference to 2,5-dimethylfuran as an internal standard. [c] Isolated yield of major diastereomer (>95:5 d.r.). [d] *ee* determined by chiral HPLC or chiral GC analysis.

and inorganic bases showed that caesium carbonate was optimal in the system (entries 1–3), and variation of the solvent showed that THF provided the best yield of the desired product (entries 3–6), with similar diastereoselectivity (approximately 75:25) observed in all cases. While β-lactone **3** was stable to work-up and could be directly isolated in moderate purity it was unstable to further purification by chromatography. To provide stable, isolable products numerous ring-opening procedures were investigated,[19] and ring-opening with allylamine provided the chromatographically stable β-hydroxyamide product. Under these conditions the desired product **4** was isolated as a single diastereomer in 57% yield and 99% *ee* (entry 7). Variation of the perfluorinated group showed that the pentafluoroethyl derivative provided a dramatic increase in diastereoselectivity, giving **5** in 74% yield and 96% *ee* (entry 8). Similarly impressive diastereo- and enantioselectivity was obtained by using a perfluorobutyl ketone (entry 9).

Next, β-lactone ring-opening with a series of nucleophiles was screened under the optimised reaction conditions (Table 2). Using the *p*-BrC_6H_4 pentafluoroethyl ketone,

Table 2. Formal [2+2] cycloadditions with perfluorinated ketones and α-aroyloxyaldehydes; ring-opening with a variety of nucleophiles.



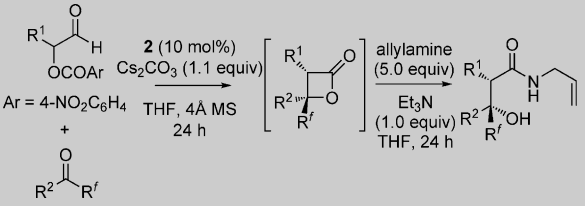
Product yield [%][a] d.r.,[b] *ee*[c]	Product yield [%][a] d.r.,[b] *ee*[c]	Product yield [%][a] d.r.,[b] *ee*[c]
7, 80% yield 94:6 d.r., 96% *ee*	**8**, 75% yield 92:8 d.r., 89% *ee*	**9**, 70% yield 92:8 d.r., 94% *ee*
10, 81% yield 90:10 d.r., 99% *ee*	**11**, 50% yield[d] 88:12 d.r., 97% *ee*	**12**, 75% yield >95:5 d.r., 89% *ee*

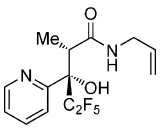
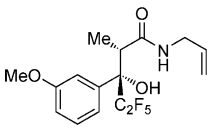
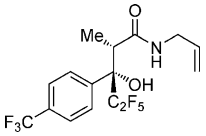
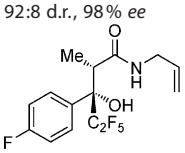
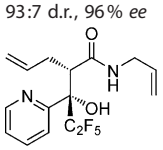
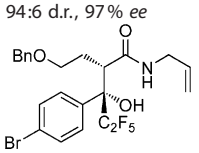
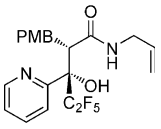
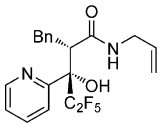
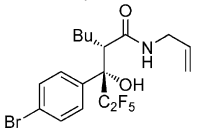
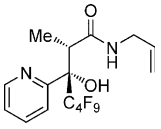
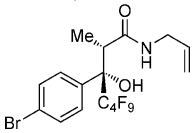
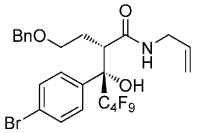
[a] Isolated yield of major diastereomer (>95:5 d.r.). [b] d.r. determined by analysis of the crude ^{1}H NMR spectra. [c] *ee* determined by chiral HPLC or chiral GC analysis. [d] 15 equivalents of *N,O*-dimethylhydroxylamine were used.

a number of different amine nucleophiles proved amenable, including ammonia, benzylamine and secondary amines such as pyrrolidine forming products **8**–**10** in high yield and excellent diastereo- and enantioselectivity.[20] *N,O*-dimethylhydroxylamine could also be used allowing access to Weinreb amide **11**. The *p*-BrC_6H_4-substituted allyl amide **7** provided unambiguous determination of the relative and absolute configuration of this molecular class through X-ray crystallographic analysis.[21] The *p*-BrC_6H_4 perfluorobutyl ketone also proved reactive with secondary amines, with the corresponding morpholine amide **12** accessed in excellent yield and selectivity (Table 2).

To further expand the versatility of this methodology, variation of the aromatic group within the pentafluoroethyl ketone was examined, with some interesting reactivity patterns noted (Table 3). Substitution of the aromatic ring with functional groups with a negative Hammett σ constant[22] led to a dramat-

Table 3. Formal [2+2] cycloadditions with perfluorinated ketones and a variety of α-aroyloxyaldehydes; ring-opening with allylamine.



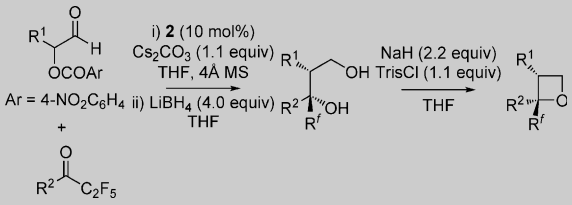
Product yield [%][a] d.r.,[b] *ee*[c]	Product yield [%][a] d.r.,[b] *ee*[c]	Product yield [%][a] d.r.,[b] *ee*[c]
 **13**, 63% yield 92:8 d.r., 98% *ee*	 **14**, 64% yield 93:7 d.r., 96% *ee*	 **15**, 86% yield 94:6 d.r., 97% *ee*
 **16**, 58% yield 92:8 d.r., 95% *ee*	 **17**, 79% yield >95:5 d.r., 98% *ee*	 **18**, 56% yield 90:10 d.r., 95% *ee*
 **19**, 51% yield 93:7 d.r., 94% *ee*	 **20**, 50% yield 93:7 d.r., 98% *ee*	 **21**, 63% yield 92:8 d.r.[d]
 **22**, 86% yield >95:5 d.r., 96% *ee*	 **23**, 81% yield >95:5 d.r., 97% *ee*	 **24**, 55% yield >95:5 d.r., 95% *ee*

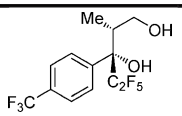
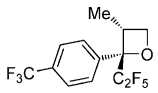
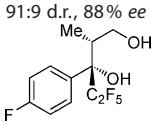
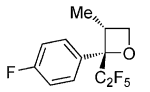
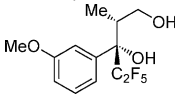
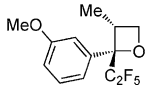
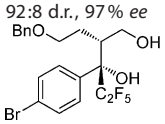
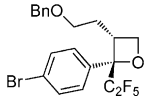
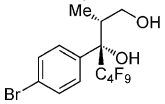
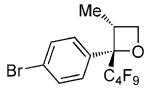
[a] Isolated yield of major diastereomer (>95:5 d.r.) [b] d.r. determined by analysis of the crude ^{1}H NMR spectra. [c] *ee* determined by chiral HPLC or chiral GC analysis. [d] *ee* could not be determined by chiral HPLC or chiral GC.

ic decrease in conversion (60% with *p*-MeC_6H_4, no observed reactivity with *p*-$MeOC_6H_4$ and *p*-$Me_2NC_6H_4$). However, the incorporation of substituents with a positive Hammett σ value (*p*-BrC_6H_4, *p*-FC_6H_4, *p*-$F_3CC_6H_4$ and *m*-$MeOC_6H_4$) were all tolerated, giving the corresponding β-hydroxyamides in good yield, with excellent diastereo- and enantioselectivity. 2-Pyridyl pentafluoroethyl ketones also proved reactive in this system, allowing the introduction of heterocyclic structures into the products (**13**–**16**).[23] A variety of different α-aroyloxyaldehydes could be utilized in this process, introducing functionality such as protected oxygen substitutents, allyl groups and *p*-methoxybenzyl (PMB) groups, with all of the desired products produced in good yield with excellent diastereo- and enantioselectivity (**17**–**21**). Furthermore, selected examples with perfluorobutyl-substituted ketones showed this methodology could be expanded to this class of ketones. Functionalized α-aroyloxyaldehydes, heteroaromatic groups and aromatic ring substitution were all tolerated, with the products synthesized in good yield with excellent enantioselectivity (**22**–**24**).

Having explored the scope of this process, derivatization of the β-lactone intermediates into perfluorinated oxetanes was investigated. NHC-catalyzed formal [2+2] cycloaddition, followed by reduction with lithium borohydride gave isolable diols **25**, **27**, **29**, **31** and **33** as single diastereoisomers after purification (Table 4). Treatment of these diols with sodium hydride and trisyl chloride subsequently allowed access to the corresponding oxetanes in excellent yield as a single diastereomer (**26**, **28**, **30**, **32**, **34**). This procedure tolerates *p*-BrC_6H_4, *p*-$F_3CC_6H_4$, *p*-FC_6H_4 and *m*-$MeOC_6H_4$ substituents, with the products isolated in good yield, and excellent diastereoselectivity

Table 4. Oxetane synthesis via a formal [2+2] cycloaddition, reduction and subsequent ring closure.

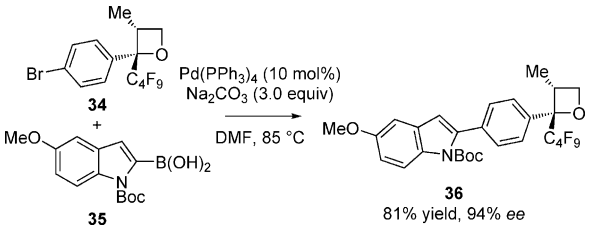


Alcohol yield %[a] d.r.,[b] *ee*[c]	Oxetane yield %[a] d.r.[b]
 **25**, 63% yield 91:9 d.r., 88% *ee*	 **26**, 89% yield >95:5 d.r.
 **27**, 53% yield 91:9 d.r., 94% *ee*	 **28**, 99% yield >95:5 d.r.
 **29**, 63% yield 92:8 d.r., 97% *ee*	 **30**, 96% yield >95:5 d.r.
 **31**, 51% yield 89:11 d.r., 94% *ee*	 **32**, 78% yield >95:5 d.r.
 **33**, 64% yield >95:5 d.r., 94% *ee*	 **34**, 91% yield >95:5 d.r.

[a] Isolated yield of major diastereomer (>95:5 d.r.). [b] d.r. determined by analysis of the crude ^{1}H NMR spectra. [c] *ee* determined by chiral HPLC or chiral GC analysis.

(>95:5 d.r.). Variation of the α-aroyloxyaldehyde was also tolerated as well as a perfluorobutyl-substituted ketone, with oxetanes **32** and **34** produced in good yield as a single diastereomer (Table 4).[24]

The highly functionalized nature of the oxetane products offers many possible opportunities for further manipulation. To confirm the ability of these products to undergo such transformations oxetane **34** (derived from diol **33**, 94% *ee*) was subjected to Suzuki–Miyaura coupling conditions using $[Pd(PPh_3)_4]$ (10 mol%) and boronic acid **35**, giving **36** in 81% yield and 94% *ee* (Scheme 3). This derivatization also confirms the enantiointegrity of the oxetane products generated within this process.



Scheme 3. Derivatization of oxetane **34** under Suzuki–Miyaura conditions.

In summary, the first NHC-catalyzed redox formal [2+2] cycloaddition from α-aroyloxyaldehydes has been developed. This methodology allows access to β-hydroxycarbonyl compounds following ring-opening in excellent yield, diastereo- and enantioselectivity. Through a reductive ring-opening and subsequent cyclization, a number of fluorinated oxetanes can be accessed in good yield as a single diastereomer over two steps. Derivatization of one of these oxetanes has confirmed no erosion of *ee* in the cyclization process. Current research within this laboratory is focused on developing alternative novel asymmetric processes using α-aroyloxyaldehydes in NHC redox catalysis and other methodologies.

Acknowledgements

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Keywords: Lewis base · N-heterocyclic carbene · organocatalysis · oxetane · pentafluoroethyl

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tion in *ee* and d.r. through epimerisation or retro-cycloaddition/cycloaddition process cannot be ruled out.
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[24] The *ee* of oxetanes **26**, **28**, **30**, **32** and **34** could not be directly established by either chiral HPLC or GC analysis. However, the *ee* of **34** was confirmed by derivatization (Scheme 3), confirming the enantiointegrity of the oxetanes generated in this protocol.

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