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Tetrahedron: *Asymmetry* 16 (2005) 2341–2347

Recyclable supports for stereoselective 1,3-dipolar cycloadditions: application of a fluorous oxazolidinone chiral auxiliary

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Received 25 May 2005; accepted 31 May 2005

Abstract—The utility of a new fluorous-supported chiral auxiliary was tested using a series of catalyzed and uncatalyzed 1,3-dipolar cycloaddition reactions with diphenylnitrone. The yields and selectivities of the cycloadducts compare favourably with those obtained using the conventional Evans-type auxiliaries, while purification was greatly assisted by using fluorous solid phase extraction. Following characterization, the cycloadducts were released from the auxiliaries by reductive cleavage. The auxiliary was readily refunctionalized and reused in subsequent cycloaddition reactions, with no deterioration of the observed yields or selectivities.

1. Introduction

Chiral oxazolidin-2-ones remain among the most widely used auxiliaries in modern stereoselective synthesis. In many cases, chiral auxiliaries offer the most convenient and highly selective routes for asymmetric transformations.[1]

A number of supported oxazolidinone chiral auxiliaries have been reported.[2] While the preparation of such compounds is more complex than the published routes to the traditional Evans' auxiliaries,[3] this additional investment may be mitigated by the recovery and reuse of the supported chiral material. The use of an effective support also opens the possibility of applying oxazolidinone auxiliaries in diversity-orientated, high-throughput and automated syntheses.

Insoluble polymers have been the mainstay of supported synthesis,[4] while soluble polymers, such as poly(ethyleneglycol) or non-crosslinked polystyrene, have also been widely used.[5] Polymer-supported oxazolidinone chiral auxiliaries have been used successfully in asymmetric alkylation,[6] aldol,[7] Diels–Alder[8] and 1,3-dipolar cycloaddition reactions.[9] Even so, many of these supported chiral auxiliaries have encountered problems associated with the polymeric supports chosen. Frequently, polymer-supported chiral auxiliary systems have afforded inconsistent yields and/or levels of stereoselectivity compared to the analogous solution-phase reactions.[2,9a,b,10] There have also been problems with recycling them, due to degradation or modification of the auxiliary or the support during the reaction.[6a,9a] Furthermore, monitoring the progress of a polymer-supported reaction, or fine-tuning the reaction conditions is not trivial. Simple laboratory techniques such as TLC or HPLC require cleavage from the support, while on-support monitoring has generally only been possible using more elaborate instrumental methods.[11]

Fluorous methods have recently emerged as a powerful alternative to many polymer-supported approaches.[12] Since 1997, Curran et al. have led the development of fluorous tags as soluble supports for organic synthesis.[13] They and an increasing number of other researchers have since applied fluorous synthetic methods to many organic transformations.[14] Recently, we created a new class of fluorous-supported oxazolidinone chiral auxiliary (Fig. 1). These auxiliaries have proven to be extremely robust and have afforded excellent results in both

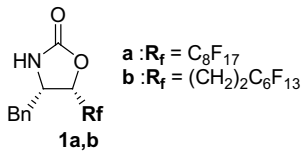

Figure 1. 4,5-Disubstituted fluorous oxazolidinone chiral auxiliaries.

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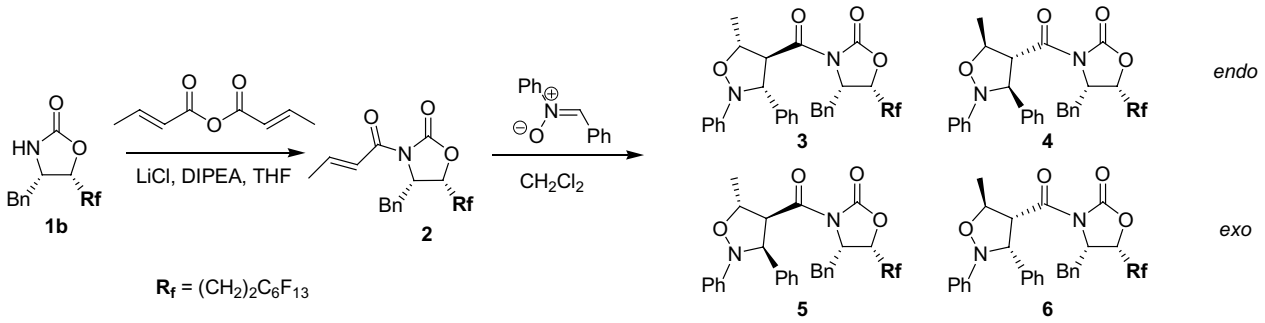
doi:10.1016/j.tetasy.2005.05.041



Scheme 1. Dipolar cycloaddition using diphenylnitrone.

titanium-mediated aldol reactions[15] and conjugate radical additions.[16] Furthermore, the products from these transformations are efficiently and rapidly purified using fluorous solid phase extraction (FSPE).

In most cases, fluorous reagents react under the same conditions and produce similar results as do their non-fluorous relatives. Nevertheless, the fluorous tag is potentially a powerful electron-withdrawing substituent, whose presence could alter the behaviour of an oxazolidinone chiral auxiliary. To fully test the extent of the perfluoroalkyl tag participation, we sought to apply auxiliary **1b** to reactions known to be extremely sensitive to changes in their reaction conditions. The 1,3-dipolar cycloaddition of nitrones[17] appeared to be an ideal system for this purpose. These reactions exhibit dramatic changes in product distribution in the presence of different catalysts, solvents or additives.[18–20] We also noted that nitrone cycloadditions to polymer-supported dipolarophiles have been studied,[9] allowing us to compare our fluorous system directly. Herein, we report the results of our experiments.

2. Results and discussion

2.1. Application of the fluorous auxiliary to 1,3-dipolar cycloadditions

Perfluoroalkyl oxazolidinone **1b**[21] was converted to crotyl derivative **2** using standard acylation protocols[22] (Scheme 1). This material was then allowed to react with diphenylnitrone, monitoring by conventional TLC. On completion, the volatile components were removed under vacuum and the residue adsorbed onto FluoroFlash™[23] before being applied to an FSPE cartridge. The cartridge was rinsed with 7:3 MeOH–H_2O to remove organic and inorganic impurities. Subsequent elution with MeOH liberated a mixture of diastereomeric cycloaddition products **3**, **4**, **5** and **6**.

By applying this convenient clean-up protocol, it was possible to rapidly explore the effect of different catalysts, solvents and additives on the diastereoselectivity of the cycloaddition (Table 1). We chose reaction conditions to parallel those employed in analogous unsupported or polymer-supported cycloadditions.[9a,19a] In each case, the product ratios were measured by HPLC on silica gel or C18 columns.

2.2. Characterization of the cycloadducts

The individual cycloaddition products **3**–**6** were obtained in pure form by preparative HPLC, allowing us to assign the stereochemistry of the newly formed isoxazolidine ring in each material.

Using ^{1}H NMR, it was possible to distinguish the two *endo* stereoisomers from the two having the *exo* geometry based on the H3′–H4′ coupling constants. Compounds **3** and **4** both showed a $J_{H3'H4'}$ of 7.5 Hz,

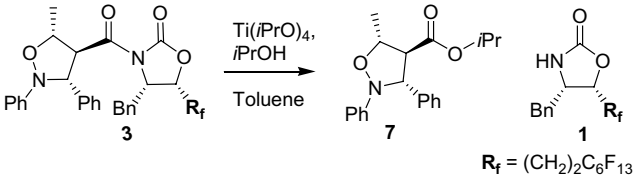
Table 1. Effect of varied reaction conditions on the diastereoselectivity of the 1,3-dipolar cycloaddition between **2** and diphenylnitrone[a]

Entry	Additive[b]	Catalyst	Time/yield (%)	*exo*:*endo*	% de *endo* (major diast)	% de *exo* (major diast)
1	—	—	14 d/92	68:32	50 (3′*R*,4′*S*,5′*R*)	76 (3′*R*,4′*R*,5′*S*)
2	—	$Mg(ClO_4)_2$	24 h/98	69:31	81 (3′*R*,4′*S*,5′*R*)	88 (3′*S*,4′*S*,5′*R*)
3	*o*-Phenanthroline	$Mg(ClO_4)_2$	2 d/87	35:65	94 (3′*R*,4′*S*,5′*R*)	54 (3′*S*,4′*S*,5′*R*)
4	—	$Sc(OTf)_3$	16 h/98	30:70	86 (3′*R*,4′*S*,5′*R*)	60 (3′*S*,4′*S*,5′*R*)
5	MS	$Sc(OTf)_3$	24 h/92	22:78	98 (3′*R*,4′*S*,5′*R*)	71 (3′*S*,4′*S*,5′*R*)
6	—	$Cu(OTf)_2$	18 h/87	60:40	84 (3′*R*,4′*S*,5′*R*)	64 (3′*S*,4′*S*,5′*R*)
7	—	$Yb(OTf)_3$	16 h/91	17:83	89 (3′*R*,4′*S*,5′*R*)	65 (3′*S*,4′*S*,5′*R*)
8	MS	$Yb(OTf)_3$	24 h/98	13:87	95 (3′*R*,4′*S*,5′*R*)	56 (3′*S*,4′*S*,5′*R*)
9[c]	MS	$Yb(OTf)_3$	24 h/58	62:38	30 (3′*R*,4′*S*,5′*R*)	53 (3′*R*,4′*R*,5′*S*)
10[d]	MS	$Yb(OTf)_3$	24 h/62	24:76	76 (3′*R*,4′*S*,5′*R*)	74 (3′*S*,4′*S*,5′*R*)

[a] Reaction conditions: CH_2Cl_2, rt, 10 mol % catalyst (where applied).
[b] Molecular sieves (4 Å) were powdered and activated under flame prior to use.
[c] Reaction performed in CH_3CN.
[d] Reaction performed in toluene.

characteristic of an *anti* relationship at these centres.[24] Conversely, compounds **5** and **6** were observed to have a $J_{H3'H4'}$ of 10.6 Hz, indicating a *syn* relationship. These results imply that **3** and **4** arose from *endo* cycloaddition, while **5** and **6** the result from an *exo* mode of attack.

The absolute stereochemistry of the isoxazolidine ring in **3** was assigned as (3′*R*,4′*S*,5′*R*) by conversion to the known isopropyl ester **7** (Scheme 2). The absolute stereochemistry of the other *endo* product **4** was then inferred as (3′*S*,4′*R*,5′*S*). The chemical conversion to assign the geometry of the two *exo* products was not possible.[19d]



Scheme 2. Lewis acid mediated transesterification.

We attempted to recrystallize both **5** and **6** to obtain material suitable for X-ray analysis. After considerable experimentation a few clear needles of **5** were obtained by slow evaporation from ethanol/water. These crystals were racemic,[25] while the pure enantiomer was obtained from the filtrate as a clear yellow oil. The presence of both enantiomers in crude **5** was consistent with the enantiomeric purity of the oxazolidinone **1b** used in these experiments.[21] The propensity for isoxazolidine cycloadducts, such as **5**, to crystallize as racemates has been observed in other cases.[26]

Given that **1b** predominantly had the 4*S*,5*R* [C(20) and C(19) in Fig. 3, respectively] geometry (98% ee), we were able to confirm that the major enantiomer of **5** indeed had the (3′*S*,4′*S*,5′*R*) geometry. The geometry of the other *exo* product **6** was then inferred to be (3′*R*,4′*R*,5′*S*).

2.3. Rationale for the observed stereoselectivity

Desimoni et al.,[19a] Faita et al.,[9b,c] and Jørgensen et al.,[19b,c] have studied the factors affecting the stereoselectivity of the 1,3-dipolar cycloaddition between various nitrone dipoles and dipolarophiles linked to oxazolidinone chiral auxiliaries.

There are two stereoselectivity issues in these reactions: diastereofacial selectivity with respect to the dipolarophile (which controls the 4′,5′ stereochemistry of the product) and *endo*/*exo* selectivity (which dictates the relative stereochemistry of the 3′ and 4′ centres). The facial selectivity of the cycloadditions (with attack on the *si* face of **2** giving rise to **3** and **5** while *re* face addition gives **4** and **6**) is controlled by chelation of the carbonyls of the dipolarophile to the metal catalyst.[9b,c,19a] The *endo*/*exo* selectivity is governed by the steric environment around the metal centre in catalyzed cycloadditions.[19b,c]

We were very pleased that cycloadditions using the fluorous chiral auxiliary **1b** followed the same trends in selectivity, indicating that the fluorous tag had a negligible electronic and steric effect on the behaviour of the auxiliary. Data in Table 1 parallel the results of cycloadditions using unsupported dipolarophiles.[19] Figure 2 draws attention to the differing behaviour of the cycloaddition performed on an insoluble polymer versus the reactions in solution. All of the solution-phase reactions predominantly afforded the (3′*S*,4′*S*,5′*R*) product in the presence of Mg^{2+}, but gave the (3′*R*,4′*R*,5′*S*) product in the absence of the metal ion. Furthermore, the fluorous auxiliary afforded a significantly higher ratio of major product to minor products than did either the soluble or insoluble polymeric supports (2.8:1 vs 1.3:1 or 1.2:1, respectively), in the presence of metal catalysts.

2.4. Recyclability of fluorous auxiliary 1b

The ability to reuse the chiral auxiliary is a key advantage to the efficiency and applicability of the supported auxiliaries. The auxiliary was tested by carrying out the cycloaddition of diphenylnitrone and dipolarophile **2** in the presence of $Mg(ClO_4)_2$ or $Sc(OTf)_3$ catalysts. Following the measurement of product ratios, the cycloadducts were reductively cleaved from the auxiliary. The free auxiliary **1b** was then acylated to reform dipolarophile **2**, which was immediately subjected to a further

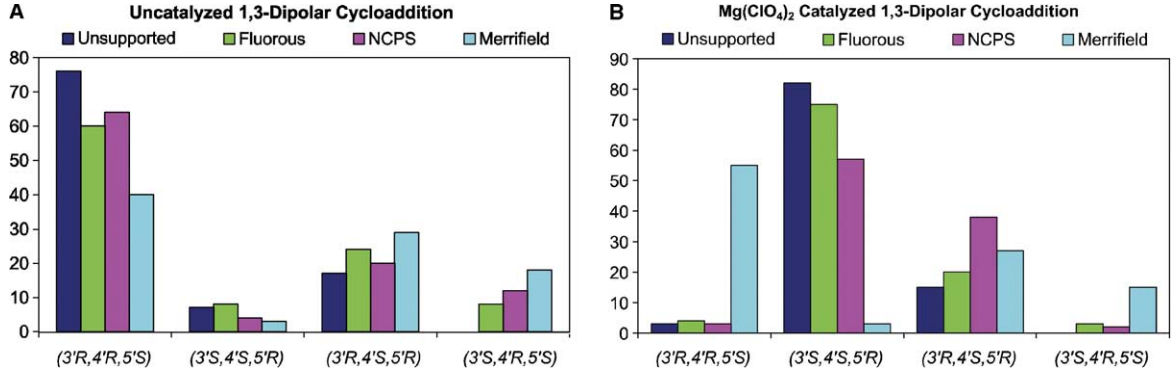


Figure 2. Comparison of diastereomer ratios from 1,3-dipolar cycloaddition of diphenylnitrone to a crotonyl dipolarophile using fluorous oxazolidinone **1b** with results using unsupported-,[19a] non-crosslinked polystyrene supported-,[9a] and Merrifield resin supported-oxazolidinone auxiliaries.[9b]

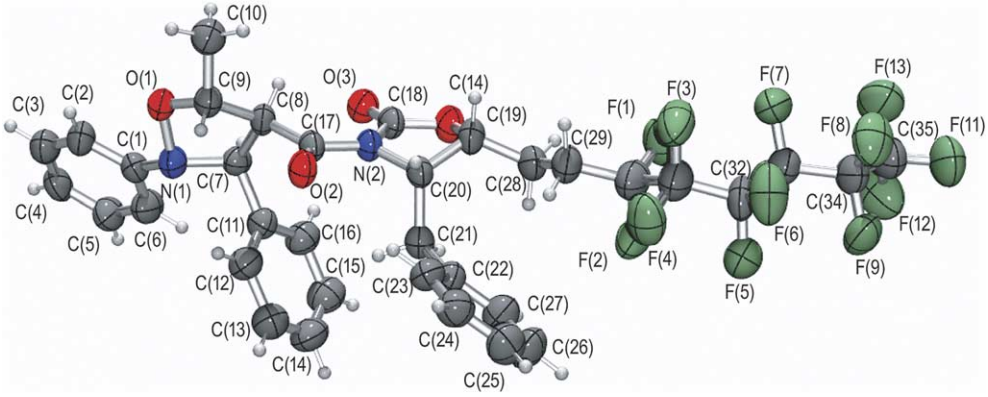


Figure 3. X-ray structure of **5**.[27] The C3′ and C4′ centres are identified as C(7) and C(8), respectively.

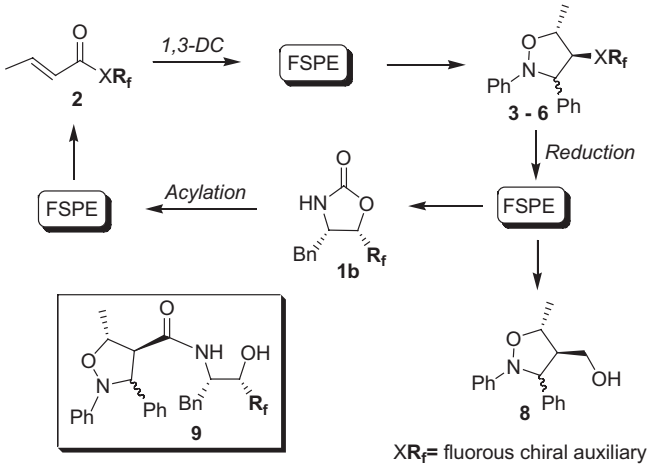


Figure 4. Recycling of **1b** in a series of 1,3-dipolar cycloadditions with diphenylnitrone.

cycloaddition. This cycle (Fig. 4) was repeated a total of five times using $Mg(ClO_4)_2$ as catalyst. We also performed three cycles using $Sc(OTf)_3$ (Table 2).

Over this series, no change in stereoselectivity or yield was observed, but a small amount of alcohol **9** was isolated. This degraded material accounted for <2% of the fluorous material recovered after five reaction cycles. The presence of this material did not affect the stereoselectivity of the cycloadditions. Alcohol **9** was easily separated from **1b** using chromatography. This demonstrates a distinct advantage of the fluorous support over polymeric materials. Modification or degradation of the chiral species on a polymer can only be rectified by cleavage and refunctionalization. The fluorous material, on the other hand, can be readily purified using conventional methods, such as flash chromatography or crystallization, allowing it to be returned to service.

Despite the formation of small amounts of **9** (which can probably be suppressed by optimizing reaction conditions), auxiliary **1b** was highly reusable. In contrast, Faita et al.[9b] found that analogous reactions performed on Wang or Merrifield resins provided significantly lower selectivity after repetitive use. They attributed this deterioration to the presence of trace water retained in the polymer matrix, which may modify the reactive geometry at the metal centre. The fluorous-supported auxiliary circumvents this problem, as trace metals, water and other impurities are removed during FSPE work-up.

Table 2. 1,3-Dipolar cycloadditions between recovered **2** and diphenylnitrone[a]

Entry	Catalyst	Cycle	*exo*:*endo*	% De *endo*	% De *exo*	Time (h)/ yield (%)
1	$Mg(ClO_4)_2$	1st	69:31	81	88	24/92
2	$Mg(ClO_4)_2$	2nd	68:32	82	88	24/90
3	$Mg(ClO_4)_2$	3rd	68:32	80	89	24/91
4	$Mg(ClO_4)_2$	4th	69:31	81	88	24/91
5	$Mg(ClO_4)_2$	5th	67:33	80	88	24/91
6	$Sc(OTf)_3$	1st	30:70	86	60	16/95
7	$Sc(OTf)_3$	2nd	32:68	87	58	16/93
8	$Sc(OTf)_3$	3rd	31:69	86	59	16/95

[a] Reaction conditions: CH_2Cl_2, rt, 10 mol % catalyst.

3. Conclusions

The reactions used herein were not necessarily highly stereoselective, but were extremely sensitive to changes in reaction conditions. This provided an ideal test of our fluorous oxazolidinone chiral auxiliary **1b**. The new auxiliary gave results that were qualitatively identical and quantitatively very similar to those obtained using unsupported oxazolidinone auxiliaries, which was not always the case with polymer-supported systems. Furthermore, **1b** was reusable without altering its efficiency in any way. We note that no attempt was made to optimize the reactions, since our purpose was to compare **1b** with existing approaches. Together with our previous data, these results suggest that our fluorous oxazolidinone should be a straightforward replacement for standard Evans-type oxazolidinones in many types of asymmetric chemistry.

4. Experimental

4.1. Materials and methods

General procedures: All melting points were measured on an Electrothermal® melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) and ^{19}F NMR (282 MHz) spectra were recorded with a Bruker Avance 300 spectrometer in $CDCl_3$ solution, unless otherwise noted. Chemical shifts for ^{1}H and ^{13}C are reported in parts per million (ppm) downfield from TMS, using residual $CHCl_3$ (7.27 ppm) or $CDCl_3$ (77.00 ppm) as internal standards. Chemical shifts for ^{19}F are reported with respect to external $CFCl_3$ (0.00 ppm). Specific rotations were measured on an Autopol® III automatic polarimeter. Preparative HPLC was performed using a Waters high throughput LC–MS–UV auto-purification system. Thin-layer chromatography was carried out on precoated (0.2 mm) Alugram® Sil G/UV silica gel plates. Fluorous solid phase extraction was performed using bulk FluoroFlash™ silica gel obtained from Fluorous Technologies Incorporated and packed into blank SPE cartridges.

Dichloromethane was distilled from calcium hydride under nitrogen prior to use. Tetrahydrofuran was distilled from sodium benzophenone under nitrogen. $Sc(OTf)_3$, $Cu(OTf)_2$ and $Yb(OTf)_3{\cdot}H_2O$ were obtained from Aldrich. $Mg(ClO_4)_2$ (Fisher) and $Yb(OTf)_3{\cdot}H_2O$ were dried at 50 °C and 0.1 Torr for 24 h prior to use. All glassware was oven dried, assembled hot and cooled under a stream of nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques.

4.2. (*E*)-(4*S*,5*R*)-4-Benzyl-3-(2′-butenoyl)-5-(1′*H*,1′*H*,2′-*H*,2′*H*-perfluorooctyl)-2-oxazolidinone, 2

Powdered and dried LiCl (0.406 g, 9.55 mmol) was added to a solution of **1b**[28] (1.000 g, 1.91 mmol) in THF (200 mL) and allowed to stir until the solution was homogeneous. *trans*-Crotonic anhydride (1.416 mL, 9.55 mmol) was then added dropwise followed by DIPEA (1.66 mL, 9.55 mmol). The solution was then heated to reflux for 24 h. After this time, the reaction was cooled, and the solvent removed under vacuum to give a crude oil. The crude material obtained (~1.5 g) was then dissolved in a minimum of Et_2O and applied to a pad of dry FluoroFlash™ (7–10 × crude weight) and driven onto the column using compressed air. The column was blown dry until no evidence of the loading solvent remained. The solid phase was then washed with 70% methanol in water (250 mL) to remove organic and inorganic impurities. Compound **2** (0.98 g, 1.657 mmol, 87% yield) was then selectively eluted by washing the column with 85% methanol in water (300 mL); R_f 0.49 (4:1 hexanes/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.16 (m, 7H), 4.91 (ddd, 1H, $^3J_1$ = 9.8 Hz, $^3J_2$ = 6.9 Hz, $^3J_3$ = 3.4 Hz), 4.53 (ddd, 1H, $^3J_1$ = 10.1 Hz, $^3J_2$ = 6.9 Hz, $^3J_3$ = 3.3 Hz), 3.13 (dd, 1H, $^3J_1$ = 14.5 Hz, $^3J_2$ = 3.2 Hz); 2.96 (dd, 1H, $^3J_1$ = 14.5 Hz, $^3J_2$ = 9.7 Hz), 2.41–2.26 (m, 1H), 2.22–2.10 (m, 1H), 1.97 (apt d, 4H, ^3J = 5.4 Hz), 1.81–1.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 21.1, 27.9, 34.0, 58.42, 77.7, 121.7, 127.1, 128.9, 129.0, 136.2, 152.5, 164.5; ^{19}F (282 MHz, $CDCl_3$) δ −81.25, −114.93, −122.36, −123.32, −123.93, −126.58; $[\alpha]_D^{25} = +13.4$ (*c* 1.00, $CHCl_3$). Anal. Calcd for formula $C_{22}H_{18}F_{13}NO_3$: C, 44.68; H, 3.07; N, 2.37. Found: C, 44.68; H, 3.30; H, 2.35.

4.3. Representative procedure for 1,3-dipolar cycloaddition

Magnesium perchlorate (0.219 g, 0.981 mmol) and **2** (0.58 g, 0.981 mmol) were dissolved in CH_2Cl_2 (0.5 mL). The solution was then stirred for 15 min at rt, after which diphenylnitrone (0.193 g, 0.981 mmol) was added. The reaction was monitored by TLC and was allowed to stir in the dark for 24 h. After this time, the crude products were adsorbed onto FluoroFlash™ fluorous-modified silica gel (~0.5 g) and applied to an FPSE cartridge charged with 5.5 g of dry FluoroFlash™. The solid phase was washed with 70% methanol in water (100 mL), removing organic and inorganic by-products. Washing the solid phase with methanol liberated cycloaddition products **3**, **4**, **5** and **6**. The diastereoselectivity was assigned by HPLC, and the individual diastereomers were separated by preparative HPLC.

4.3.1. (3′*R*,4*S*,4′*S*,5*R*,5′*R*)-4-Benzyl-3-((5′-methyl-2′,3′-diphenylisoxazolidin-4′-yl)carbonyl)-5-(1′*H*,1′*H*,2′*H*,-2′*H*-perfluorooctyl)-2-oxazolidinone, 3.

Isolated as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–6.91 (m, 15H), 5.12 (d, ^3J = 6.7 Hz, 1H), 4.90–4.84 (m, 1H), 4.79 (dd, $^3J_1$ = 7.3 Hz, $^3J_2$ = 7.3 Hz, 1H), 4.52–4.43 (m, 2H), 3.07 (dd, $^3J_1$ = 14.5 Hz, $^3J_1$ = 3.5 Hz, 1H), 2.89 (dd, $^3J_1$ = 14.5 Hz, $^3J_2$ = 9.5 Hz, 1H), 2.36–2.16 (m, 1H), 2.13–2.04 (m, 1H), 1.99–1.86 (m, 1H), 1.79–1.69 (m, 1H), 1.52 (d, ^3J = 6.7 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 18.0, 20.9, 27.8, 33.8, 58.7, 62.9, 71.8, 74.6, 79.4, 114.7, 121.8, 126.6, 127.4, 127.9, 128.6, 128.8, 128.9, 129.0, 135.5, 140.6, 151.4, 151.8, 170.3; ^{19}F (282 MHz, $CDCl_3$) δ −81.18, −114.86, −122.35, −123.30, −123.92, −126.55; $[\alpha]_D$ = +99.1 (*c* 0.8, Et_2O). Anal. Calcd for formula $C_{35}H_{29}F_{13}N_2O_4$: C, 53.31; H, 3.71; N, 3.55. Found: C, 52.93; H, 3.44; N, 3.74.

4.3.2. (3′*S*,4*S*,4′*R*,5*R*,5′*S*)-4-Benzyl-3-((5′-methyl-2′,3′-diphenylisoxazolidin-4′-yl)carbonyl)-5-(1′*H*,1′*H*,2′*H*,-2′*H*-perfluorooctyl)-2-oxazolidinone, 4. Isolated as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–6.91 (m, 15H), 5.09 (d, ^3J = 7.2 Hz, 1H), 4.93–4.85 (m, 1H), 4.68 (dd, $^3J_1$ = 7.5 Hz, $^3J_2$ = 7.4 Hz, 1H), 4.49–4.41 (m, 1H), 4.31 (dq, $^3J_1$ = 7.4 Hz, $^3J_2$ = 6.3 Hz, 1H), 3.02 (dd, $^3J_1$ = 14.4 Hz, $^3J_1$ = 4.6 Hz, 1H), 2.94 (dd, $^3J_1$ = 14.4 Hz, $^3J_2$ = 8.6 Hz, 1H), 2.37–2.23 (m, 1H), 2.22–2.05 (m, 2H), 2.00–1.88 (m, 1H), 1.53 (d, ^3J = 6.3 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 18.2, 21.3, 27.7, 33.0, 58.9, 63.1, 72.1, 74.3, 79.1, 114.7, 121.7, 126.5, 127.3, 128.0, 128.6, 128.8, 128.9, 129.0, 135.5, 140.6, 151.4, 152.1, 170.1; ^{19}F (282 MHz, $CDCl_3$) δ −81.20, −114.89, −122.34, −123.29, −123.90, −126.55; $[\alpha]_D$ = +32.8 (*c* 0.5, Et_2O). Anal. Calcd for formula $C_{35}H_{29}F_{13}N_2O_4$: C, 53.31; H, 3.71; N, 3.55. Found: C, 53.68; H, 3.98; N, 3.12.

4.3.3. (3′*S*,4*S*,4′*S*,5*R*,5′*R*)-4-Benzyl-3-((5′-methyl-2′,3′-diphenylisoxazolidin-4′-yl)carbonyl)-5-(1′*H*,1′*H*,2′*H*,-2′*H*-perfluorooctyl)-2-oxazolidinone, 5. Isolated as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–6.90 (m, 15H), 5.12 (dq, $^3J_1$ = 9.7 Hz, $^3J_2$ = 6.0 Hz, 1H), 5.10 (d, ^3J = 10.9 Hz, 1H), 4.60–4.53 (m, 1H), 4.43–4.37 (m, 1H), 4.25 (dd, $^3J_1$ = 10.7 Hz, $^3J_2$ = 9.7 Hz, 1H), 2.88 (dd, $^3J_1$ = 13.9 Hz, $^3J_1$ = 5.2 Hz, 1H), 2.78 (dd, $^3J_1$ = 13.9 Hz, $^3J_2$ = 8.4 Hz), 2.29–2.09 (m, 1H), 1.94–1.71 (m, 4H), 1.61–1.52 (m, 1H), 1.48 (d, ^3J = 6.0 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 17.1, 20.7, 27.7, 32.0, 58.2, 60.3, 71.9, 74.8, 77.7, 115.9, 122.3, 127.0, 128.4, 128.5, 128.6, 128.8, 128.9, 136.3, 138.6, 149.8, 151.9, 168.7; ^{19}F (282 MHz, $CDCl_3$) δ −81.19, −114.97, −122.36, −123.30, −123.94, −126.54; $[\alpha]_D$ = +88.5 (*c* 0.5, Et_2O). Anal. Calcd for formula $C_{35}H_{29}F_{13}N_2O_4$: C, 53.31; H, 3.71; N, 3.55. Found: C, 53.64; H, 3.60; N, 3.38.

4.3.4. (3′*R*,4*S*,4′*R*,5*R*,5′*S*)-4-Benzyl-3-((5′-methyl-2′,3′-diphenylisoxazolidin-4′-yl)carbonyl)-5-(1′*H*,1′*H*,2′*H*,-2′*H*-perfluorooctyl)-2-oxazolidinone, 6. Isolated as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.17 (m, 15H), 5.01 (dq, $^3J_1$ = 9.3 Hz, $^3J_2$ = 6.1 Hz, 1H), 4.81 (d, ^3J = 10.7 Hz, 1H), 4.35 (dd, $^3J_1$ = 10.7 Hz, $^3J_2$ = 9.3 Hz, 1H), 4.08–4.02 (m, 1H), 3.51–3.43 (m, 1H), 2.88 (dd, $^3J_1$ = 13.9 Hz, $^3J_1$ = 5.2 Hz, 1H), 2.78 (dd, $^3J_1$ = 13.9 Hz, $^3J_2$ = 8.4 Hz, 1H), 2.29–2.09 (m, 1H), 2.04–1.81 (m, 2H), 1.64–1.55 (m, 1H), 1.39 (d, ^3J = 6.1 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 17.8, 21.2, 26.8, 34.8, 58.3, 60.3, 71.8, 74.6, 78.6, 116.6, 122.8, 127.2, 128.4, 128.5, 128.6, 128.8, 129.1, 135.7, 138.5, 149.6, 152.1, 168.5; ^{19}F (282 MHz, $CDCl_3$) δ −81.17, −114.79, −122.32, −123.27, −123.86, −126.53; $[\alpha]_D$ = +27.4 (*c* 0.32, Et_2O). Anal. Calcd for formula $C_{35}H_{29}F_{13}N_2O_4$: C, 53.31; H, 3.71; N, 3.55. Found: C, 53.54; H, 3.56; N, 3.41.

4.4. (3*R*,4*S*,5*R*)-4-Isoxazolidinecarboxylic acid, 5-methyl-2,3-diphenyl-, isopropyl ester, 7

Following the procedure described in the literature,[19c] Ti(*i*PrO)$_4$ (0.074 mL, 0.254 mmol) and *i*PrOH (0.039 mL, 0.507 mmol) were added to a solution of **3** (0.02 g, 0.025 mmol) in toluene (2 mL). The reaction was then heated to reflux and left to stir for 5 h, after which the reaction was cooled and the reaction evaporated to dryness. The crude mixture was adsorbed onto FluoroFlash™ fluorous-modified silica gel (~0.1 g) and applied to an FPSE cartridge charged with 5.5 g of dry FluoroFlash™. The solid phase was washed with 70% methanol in water (150 mL), allowing **7** (0.0076 g, 0.023 mmol, 92% yield) to be isolated as a colourless oil. Washing the solid phase with methanol gave (4*S*,5*R*)-4-benzyl-5-(1′*H*,1′*H*,2′*H*,2′*H*-perfluorooctyl)-2-oxazolidinone **1b** (0.011 g, 0.021 mmol, 83% yield) as a crystalline solid. ^{1}H NMR values for **7** matched those reported in the literature. The absolute configuration was determined by chemical correlation to literature results; $[\alpha]_D$ = +43.7 (*c* 0.65, $CHCl_3$); lit. $[\alpha]_D$ = +35.[19c]

4.5. Reductive cleavage applied in recyclability study

Sodium borohydride (0.179 mL, 5.07 mmol) was dissolved in water (2 mL) and added to a solution of cycloaddition products **3**, **4**, **5** and **6** (1 g, 1.268 mmol) in THF (20 mL). The reaction was left to stir at rt for 5 h, after which the reaction was quenched with 1 M HCl (5 mL) and evaporated to dryness. The crude mixture was adsorbed onto FluoroFlash™ fluorous-modified silica gel (~0.5 g) and applied to an FPSE cartridge charged with 5.5 g of dry FluoroFlash™. The solid phase was washed with 70% methanol in water (250 mL), allowing **8** to be isolated (0.2 g, 0.743 mmol, 58.6% yield). Washing the solid phase with methanol gave (4*S*,5*R*)-4-benzyl-5-(1′*H*,1′*H*,2′*H*,2′*H*-perfluorooctyl)-2-oxazolidinone **1b** (0.59 g, 1.127 mmol, 89% yield) as a crystalline solid.

4.5.1. 5-Methyl-2,3-diphenyl-isoxazolidine-4-methanol, 8. Obtained as a mixture of stereoisomers, ^{1}H and ^{13}C NMR values matched those reported in the literature.[19b]

4.5.2. 10-((5′-Methyl-2′,3′-diphenylisoxazolidin-4′-yl)carbonylamino)-1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-11-phenyl-undecan-9-ol, 9. ^{1}H NMR (300 MHz, $CDCl_3$) 7.54–6.89 (m, 15H), 5.90 (d, ^3J = 7.3 Hz, 1H), 4.90 (d, ^3J = 8.7 Hz), 4.15 (dq, $^3J_1$ = 8.7 Hz, $^3J_2$ = 6.7 Hz, 1H), 3.93–3.87 (m, 1H), 3.34 (dd, $^3J_1$ = 8.7 Hz, $^3J_2$ = 4.1 Hz, 1H), 3.15–3.09 (m, 1H), 2.81 (dd, $^3J_1$ = 14.1 Hz, $^3J_2$ = 4.8 Hz, 1H), 2.53 (dd, $^3J_1$ = 14.1 Hz, $^3J_2$ = 11.1 Hz, 1H), 2.34 (d, ^3J = 6.5 Hz, 1H), 3.32–2.14 (m, 1H), 2.01–1.79 (m, 1H), 1.41–1.23 (m, 2H), 1.11 (d, ^3J = 6.5 Hz, 3H).

Acknowledgements

The authors thank Dr. Jim Britton and Dr. Laura Harrington at the McMaster Analytical X-ray diffraction facility for structural analysis, and Dr. Frank Schweizer for providing access to HPLC–MS. We also acknowledge the support of Fluorous Technologies Inc., and an operating grant from the Natural Sciences and Engineering Research Council of Canada.

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28. Fluorous oxazolidinone **1b** was synthesized from L-phenylalanine using a modification of the procedure previously reported. See Ref. 5 for details.