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A Fluorous-Tagged "Safety Catch" Linker for Preparing Heterocycles by Ring-Closing Metathesis

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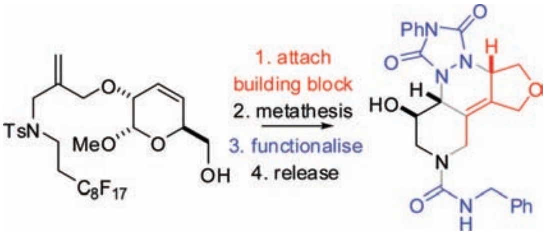
ABSTRACT



A fluorous-tagged "safety catch" linker is described for the synthesis of heterocycles with use of ring-closing metathesis. The linker facilitiates the purification of metathesis substrates, the removal of the catalyst, the functionalization of the products, and the release of only metathesis products. The synthesis of a range of heterocycles is described.

Ring-closing metathesis has revolutionalized organic synthesis.[1] Ruthenium complexes are particularly functional group tolerant,[2] but the catalyst residues often need to be scavenged.[3] Recently, we developed a fluorous-tagged linker for synthesizing heterocycles by metathesis but a fluorous-tagged catalyst was needed to allow easy product purification.[4] We now describe a fluorous-tagged "safety catch"[5] linker that facilitates the synthesis, purification, and functionalization of metathesis products without the use a fluorous-tagged catalyst (Scheme 1). We use the term "linker" to describe compounds (e.g., **1**) which are functionalized to yield metathesis substrates (e.g., **2**).

It was envisaged that functionalization of **1** (→ **2**) would be followed by removal of excess reagents by fluorous-solid phase extraction[6] (F-SPE). Initiation of a metathesis cascade would be expected at the terminal alkene[7] of **2** (→ **3**). Cyclization (→ **4**) would be followed by a second ring-closing metathesis (→ **5**) in which a catalytically active methylene complex was regenerated.[8] Crucially, the product **5** would still be fluorous-tagged; F-SPE would thus allow

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(1) (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (b) Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* **2007**, *63*, 3919. (c) Gradillas, A.; Péres-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086.

(2) Grubbs, R. H. *Handbook of Metathesis*, Wiley-VCH: Weinheim, Germany, 2003.

(3) For example, see: (a) Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411. (b) Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137. (c) Galan, B. R.; Kalbarczyk, K. P.; Szczepankiewicz, S.; Keister, J. B.; Diver, S. T. *Org. Lett.* **2007**, *9*, 1203. (d) Matsugi, M.; Curran, D. P. *J. Org. Chem.* **2005**, *70*, 1636. (e) Yao, Q.; Zhang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 74.

(4) (a) Leach, S. G.; Cordier, C. J.; Morton, D.; McKiernan, G. J.; Warriner, S.; Nelson, A. *J. Org. Chem.* **2008**, *73*, 2752. (b) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 104.

(5) Patek, M.; Lebl, M. *Biopolymers* **1999**, *47*, 353.

(6) Zhang, W.; Curran, D. P. *Tetrahedron* **2006**, *62*, 11837.

(7) (a) Ulman, M.; Grubbs, R. H. *Organomet.* **1998**, *17*, 2484. (b) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912.

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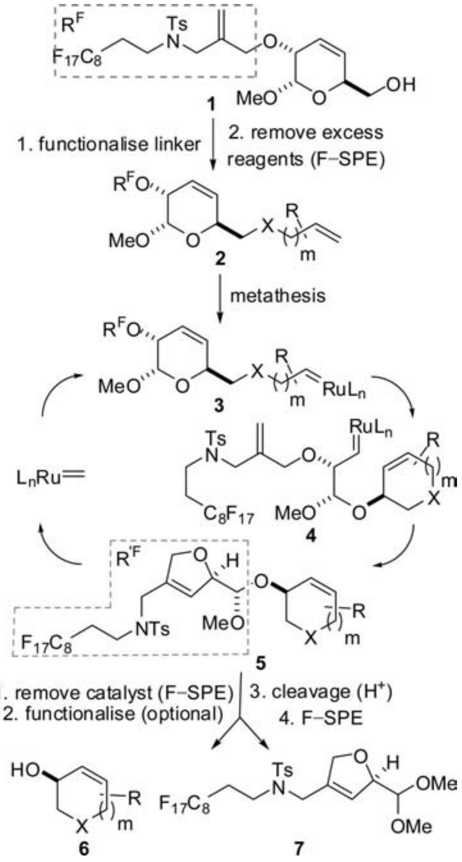
Scheme 1. Design of the Fluorous-Tagged “Safety Catch” Linker **1**

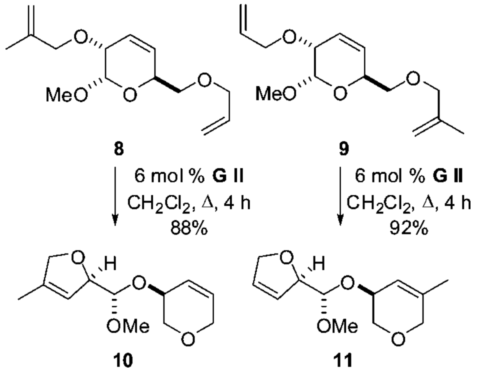


removal of the metathesis catalyst and removal of the excess reagents in subsequent functionalization steps. Finally, acetal cleavage would release only metathesis products (e.g., **6**) (and not unreacted substrates such as **2**) from the fluorous tag. The fluorous-tagged linker **1** was, therefore, designed to be a “safety catch”[5] linker since the cleavage step should release only metathesis products.

To validate the design, we prepared the trienes **8** and **9** from a known glucose derivative (see the Supporting Information). Treatment of **8** and **9** (4 mM in CH_2Cl_2) with 6 mol % Grubbs’s second generation catalyst gave the expected metathesis products **10** and **11** (Scheme 2). Thus, irrespective of the initiation site,[7] the metathesis cascade proceeded smoothly, cleaving the central dihyropyran ring. The study validated the “safety catch” linker design since hydrolysis of the resulting acyclic acetals would yield the required dihydropyran products.

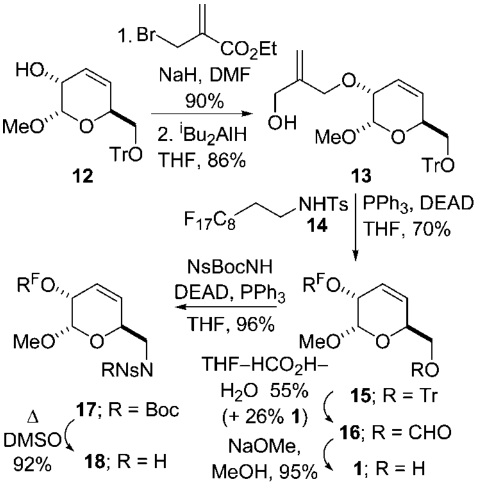
Scheme 3 describes the synthesis of the linkers **1** and **18**. Reaction of the anion of **12** with ethyl α-bromomethyl acrylate,[9] and reduction, gave the allylic alcohol **13**. A Fukuyama−Mitsunobu reaction[10] between **13** and the sulfonamide[4] **14**, and deprotection, gave the fluorous-tagged linker **1**. Finally, Fukuyama−Mitsunobu reaction with Ns-BocNH, and deprotection, gave the fluorous-tagged sulfonamide **18**.

Scheme 2. Validation of the Design of the Linker **1**[a]



[a] **GII** is Grubbs’s second generation catalyst.

Scheme 3. Preparation of the Fluorous-Tagged Linkers **1** and **18**[a]



[a] For the definition of R^F, see Scheme 1.

The linkers **1** and **18** were functionalized with a range of reactants (see Figure 1, Table 1, and the Supporting Information). Thus, the substrates were prepared by using the Fukuyama−Mitsunobu reaction,[10] allylation, silaketal formation,[11] or esterification. In general, the fluorous-tagged products were purified by F-SPE alone, and the purities were determined by HPLC.

The cascade reactions of a range of the metathesis substrates were successful (Table 1). Six- and seven-

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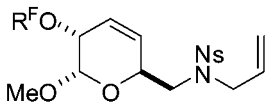
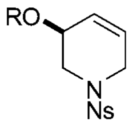
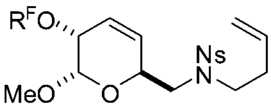
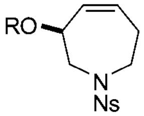
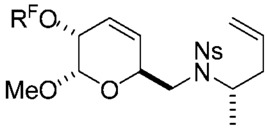
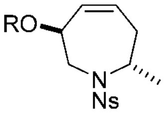
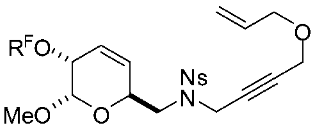
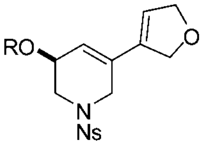
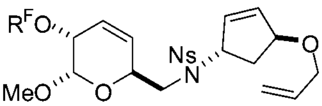
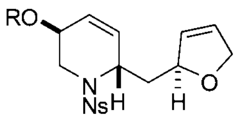
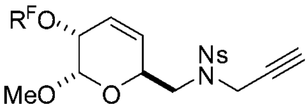
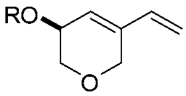
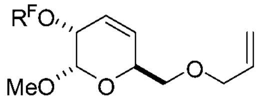
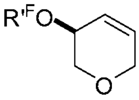
(8) Moriggi, J.-D.; Brown, L. J.; Castro, J. L.; Brown, R. C. D. *Org. Biomol. Chem* **2004**, *2*, 835.

(9) Villieras, J.; Rambaud, M. *Org. Synth.* **1988**, *66*, 220.

(10) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

(11) Cordier, C.; Morton, D.; Leach, S.; Woodhall, T.; O‘Leary-Steele, C.; Warriner, S.; Nelson, A. *Org. Biomol. Chem.* **2008**, *6*, 1734.

Table 1. Heterocycle Synthesis by Functionalization of the Linker, Metathesis, and Release (See Scheme 1 for the Definitions of R^F and R′^{F})

		functionalisation		metathesis			cleavage	
entry	linker (reactant, method[a])	product[b]	yield[c] / %	method[a] (catalyst mol %)	yield[c] / %	product[b]	method[a]	product [yield[c] / %]
1	**1** (**19**, A)		87[d] (93[e])	B (3 × 5)	90[d] (94[e])	 **26** (R = R′^{F})	C	**26** (R=H) [70]
2	**1** (**20**, A)		98[d] (92[e])	B (3 × 5)	55 (80,[d] 69[e])	 **27** (R = R′^{F})	C	**27** (R=H) [77]
3	**1** (**21**, A[f])		26	B (2 × 5)	98[d] (85[e])	 **28** (R = R′^{F})	C	**28**(R=H) [62] (93,[d]72[e])
4	**1** (**22**, A)		98	B (2 × 5)	41	 **29** (R = R′^{F})	C	**29** (R=H) [67]
5	**18** (**23**, A)		>98[d] (83[e])	B (6 × 5)	87	 **30** (R = R′^{F})	C	**30** (R=H) [35]
6	**18** (**24**, A)		>98[d] (84[e])	B[g] (5)	53 (83,[d] 65[e])	 **31** (R = R′^{F})	C	**31** (R=H) [23]
7	**1** (**25**, D)		72[d] (93[e])	B (2 × 5)	51	 **32**	*h*	–

[a] Method A: reactant (4 equiv), PPh$_3$ (4 equiv), DEAD (4 equiv), THF, rt then F-SPE. Method B: (i) Hoveyda−Grubbs second generation catalyst, CH$_2$Cl$_2$, reflux; (ii) P(CH$_2$OH)$_3$, Et$_3$N then silica; (iii) F-SPE. Method C: 3% TFA in CH$_2$Cl$_2$, rt then F-SPE. Method D: (i) NaH, THF, 0 °C; (ii) allyl bromide, rt; (iii) MeOH then F-SPE; [b] See Scheme 1 for the definitions of R^F and R′^{F}. [c] Unless otherwise stated, isolated yield of product. [d] Mass of product after F-SPE. [e] Purity (%) determined by HPLC after F-SPE. [f] 10 equiv of the sulfonamide, PPh$_3$, and DEAD were used. [g] In the presence of an ethylene atmosphere. [h] Not undertaken.

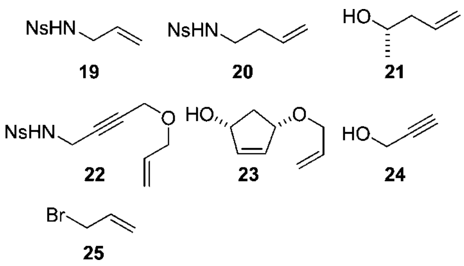


Figure 1. Reactants used to derivatize the linkers **1** and **18**.

membered nitrogen and oxygen heterocycles were formed in good to excellent yield. In the case of the terminal alkyne substrate (entry 6), the reaction was performed under an ethylene atmosphere,[12] and a 53% yield of the fluorous-tagged product **31** (R = R′^{F}) was obtained. More complex cascade reactions in which two new heterocyclic rings were formed were also successful (entries 4 and 5). Unlike with our previous linker,[4] it was not possible to prepare eight- or nine-membered heterocycles (see the Supporting Information for the substrates studied); instead, dimerization was competitive with cyclization and, hence, release from the linker. Six metathesis products [**26**−**31** (R = H)] were released directly from the linker by treatment of the correponding metathesis products with 3% TFA in CH$_2$Cl$_2$ (entries 1−6, Table 1).

The metathesis products could also be functionalized before release from the fluorous tag (see Table 2 and Figure 2). In each case, the excess reagents were removed by F-SPE only. Thus, removal of the *o*-nitrophenylsulfonyl group from **26** (R = R′^{F}), derivatization, and release from

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[12] Lloyd-Jones, G. C.; Margue, R. G.; de Vries, J. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7442.

Table 2. Functionalisation of the Metathesis Products and Release from the Fluorous Tag[a]

entry	starting material	purity/%	functionalization method[b]	product	mass recovery[c]/% (purity[d]/%)	cleavage method[b]	product	yield[e]/%
1	**26** (R = R′^{F})	94	A	**33** (R = R′^{F})	87 (>90)	B	**33** (R = H)	82
2	**26** (R = R′^{F})	94	C	**34** (R = R′^{F})		B	**34** (R = H)	67[f]
3	**26** (R = R′^{F})	>99	E	**35** (R = R′^{F})		B	**35** (R = H)	57[f]
4	**29** (R = R′^{F})	>99	D	**36** (R = R′^{F})	86 (87)	B	**36** (R = H)	59
5	**36** (R = R′^{F})	87	A	**37** (R = R′^{F})	79 (>95)	B	**37** (R = H)	67

[a] See Scheme 1 for the definition of R′^{F}. [b] Method A: (i) PhSH, DBU, MeCN; (ii) BnNCO; (iii) F-SPE. Method B: (i) 3% TFA in CH_2Cl_2; (ii) F-SPE. Method C: (i) PhSH, DBU, MeCN; (ii) Ac_2O, pyridine; (iii) F-SPE. Method D: (i) 4-phenyl-[1,2,4]-triazole-3,5-dione, CH_2Cl_2; (ii) F-SPE. Method E: (i) PhSH, DBU, MeCN; (ii) DMAP and isoxazole-5-carbonyl chloride; (iii) F-SPE. [c] Mass of product after F-SPE only. [d] Purity (%) determined by HPLC after F-SPE only. [e] Isolated yield of purified product. [f] Isolated yield of product over 2 steps.

the fluorous tag yielded the tetrahydropyridines **33** (R = H), **34** (R = H), and **35** (R = H) (entries 1−3). Alternatively, the diene **29** (R = R′^{F}) underwent efficient Diels−Alder reaction with 4-phenyl-[1,2,4]-triazole-3,5-dione to yield **36** (R = R′^{F}): the resulting adduct could either be released directly from the fluorous tag [→ **36** (R = H), entry 4] or after deprotection and derivatization [→ **37** (R = H), entry 5].

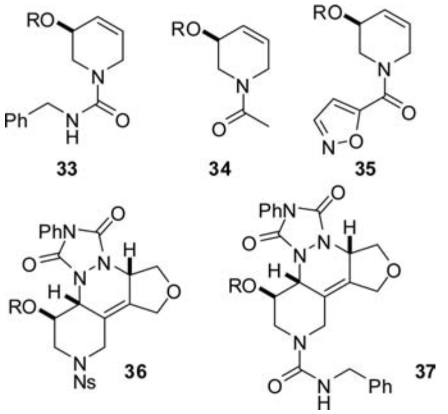

Figure 2. Derivatized metathesis products after release from the fluorous tag, R = H.

In summary, we have developed a linker for the synthesis of arrays of heterocylic products using metathesis cascade reactions. The design of the fluorous-tagged linker allowed (a) easy purification of metathesis substrates; (b) easy removal of the catalyst from the metathesis products; (c) functionalization of the products before release; and (d) the release of only metathesis products.

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Supporting Information Available: Details of all experimental procedures, including unsuccessful metathesis substrates, and NMR spectra for all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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