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An Efficient Synthesis of Nitroalkenes by Alkene Cross Metathesis: Facile Access to Small Ring Systems

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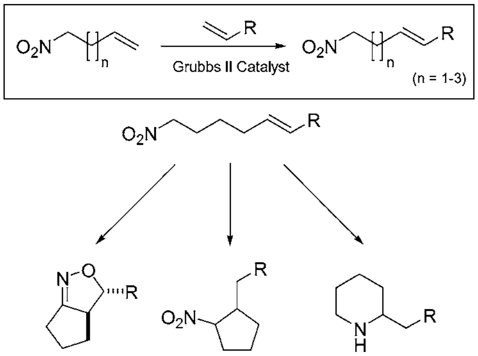
ABSTRACT



A synthesis of highly functionalized nitroalkenes is reported that utilizes a cross metathesis (CM) reaction between simple aliphatic nitro compounds and a range of substituted alkenes. This chemistry offers a simple and attractive route to nitroalkenes that would otherwise be difficult to prepare, and that have a very useful application as precursors to a variety of heterocyclic entities.

The chemistry of the nitro group is very wide-ranging in organic synthesis.[1] Carreira has recently demonstrated that optically pure nitroalkanes can be converted, while retaining optical integrity, into aldoximes, which are convenient precursors of nitriles[2] and nitrile oxides.[3] Aside from the nitroaldol (Henry) reaction, the introduction of a nitro group is commonly effected by the displacement of a halide with a nitrite anion,[4] but this reaction can often be unreliable with sensitive or highly functionalized haloalkanes. Addressing this challenge, Ballini and co-workers have recently shown that the use of silver nitrite in aqueous media[5] is a more robust and effective protocol, in certain cases, than the use of sodium or silver nitrite in solvents such as dimethylformamide or dimethyl sulfoxide.

Alkene metathesis[6] has become a fundamental carbon−carbon bond-forming tool for organic chemists, seeing wide application in many areas, including total syntheses of complex natural products and polymer chemistry.

In particular, the well-known cross metathesis (CM) reaction[7] has been extensively employed to form a range of substituted alkenes. The development of potent catalysts[8] to execute this type of transformation, coupled with an ever

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[1] Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751.

[2] Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 612.

[3] (a) Torsell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: Weinhelm, Germany, 1988; (b) Larsen, K. E.; Torsell, K. B. G. *Tetrahedron* **1984**, *40*, 2985.

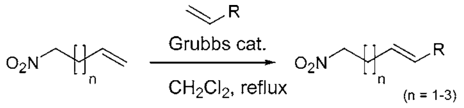
[4] Kornblum, N.; Larson, H. O.; Blackwood, R. K.; Mooberry, D. D.; Oliveto, E. P.; Graham, G. E. *J. Am. Chem. Soc.* **1956**, *78*, 1497.

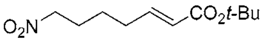
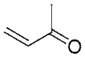
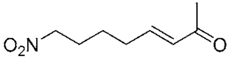
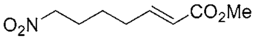
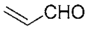
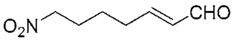
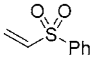
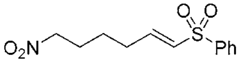
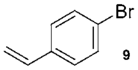
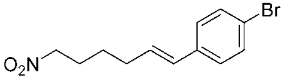
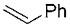
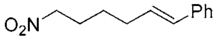
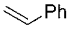
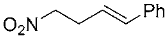
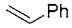
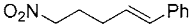
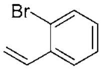
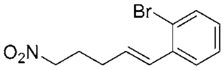
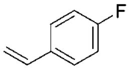
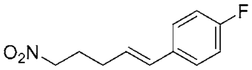
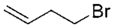
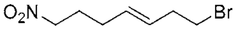
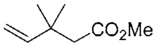
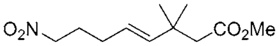
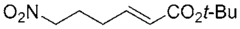
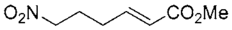
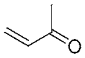
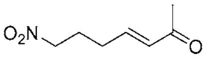
[5] Ballini, R.; Barboni, L.; Giarlo, G. *J. Org. Chem.* **2004**, *69*, 6907.

[6] (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

10.1021/ol070557k CCC: $37.00

Table 1. Functionalized Aliphatic Nitro Compounds by CM



nitroalkene		CM partner	CM product[a]		yield (%)
n=3	**1**			**2**	85
n=3	**1**			**5**	73
n=3	**1**			**6**	76
n=3	**1**			**7**	51
n=3	**1**			**8**	50
n=3	**1**	 **9**		**10**	65
n=3	**1**			**11**	69
n=1	**3**			**12**	68
n=2	**4**			**13**	63
n=2	**4**			**14**	68
n=2	**4**			**15**	69
n=2	**4**			**16**	79
n=2	**4**			**17**	73
n=2	**4**			**18**	69
n=2	**4**			**19**	75
n=2	**4**			**20**	73

[a] (*E*) exclusively (^{1}H NMR).

improving model to understand and predict selectivity,[9] makes this reaction a powerful tool for the introduction of a plethora of functionality. To illustrate, CM has lately been reported with amide- and urea-functionalized olefins[10] and also with vinyl boronates.[11] In addition to instances of the application of CM to the construction of natural products, a number of accounts have amassed in the recent literature of CM being used in sequential catalysis and tandem processes.[12]

In our laboratory we have for some time been interested in isoxazolines,[13,14] and also more broadly in the general area of nitrile oxide cycloaddition chemistry.[14,15] As such, we have required an efficient method for the production of highly substituted nitro compounds.

Hitherto, to our knowledge no example of a cross metathesis reaction to form substituted aliphatic nitro olefins has been reported.

When 6-nitrohex-1-ene **1** was treated with *tert*-butyl acrylate and Grubbs second generation catalyst[16] in boiling

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(7) (a) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (b) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58.

(8) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

(9) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(10) Formentín, P.; Gimeno, N.; Steinke, J. H. G.; Vilar, R. *J. Org. Chem.* **2005**, *70*, 8235.

(11) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031.

(12) Recent examples: (a) Beligny, S.; Eibauer, S.; Maechling, S.; Blechert, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1900. (b) Gebauer, J.; Blechert, S. *J. Org. Chem.* **2006**, *71*, 2021. (c) Finnegan, D.; Seigal, B. A.; Snapper, M. L. *Org. Lett.* **2006**, *8*, 2603. (d) Hodgson, D. M.; Angrish, D.; Labande, A. H. *Chem. Commun.* **2006**, *6*, 627. (e) Lee, C.-H. A.; Loh, T.-P. *Tetrahedron Lett.* **2006**, *47*, 809. (f) Gebauer, J.; Dewi, P.; Blechert, S. *Tetrahedron Lett.* **2005**, *46*, 43.

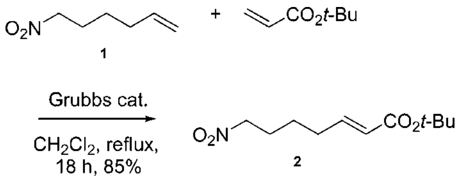
(13) Pennicott, L.; Lindell, S. *Synlett* **2006**, *3*, 463.

(14) Parsons, P. J.; Charles, M. D.; Harvey, D. M.; Sumoreeah, L. R.; Shell, A.; Spoors, G.; Gill, A. L.; Smith, S. *Tetrahedron Lett.* **2001**, *42*, 2209.

(15) (a) Fédou, N. M.; Parsons, P. J.; Viseux, E. M. E.; Whittle, A. J. *Org. Lett.* **2005**, *7*, 3179. (b) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (c) Knight, J.; Parsons, P. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 979.

dichloromethane, the α,β-unsaturated ester **2** was formed in 85% isolated yield (Scheme 1).

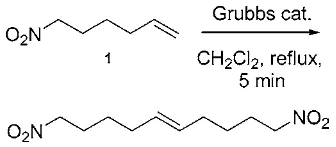
Scheme 1. CM Involving an Aliphatic Nitro Compound



By application of the same methodology we were able to prepare a range of substituted nitroalkenes (Table 1), finding that the aliphatic nitro group neither interfered with the CM process nor deactivated the catalyst.

The helpful report on selectivity in CM recently published by Grubbs and co-workers[9] classifies terminal alkenes bearing a variety of functionality according to their readiness to participate in a CM reaction, and provides an illustration of the vast functional group tolerance of this process. This highly developed model allows the synthetic chemist, by consideration of relative rates of homodimerization under the metathesis conditions, to prepare the desired CM product in high yield. Due to a rapid rate (10−15 min) of homodimerization, we suggest that 6-nitrohex-1-ene **1** should be classified as a type I alkene according to Grubbs' model (Scheme 2). Indeed, such a designation is also corroborated by the observed activity of **1** under CM conditions with the substituted olefins reported in Table 1.

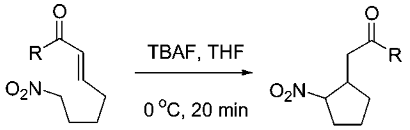
Scheme 2. Homodimerization of 6-Nitro-1-hexene

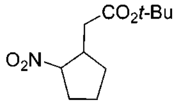
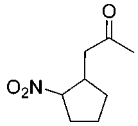


This CM methodology offered us an expedient route to the substituted aliphatic nitro compounds we desired. In addition, we have also observed that the aforementioned CM products can provide facile access to a number of extremely useful cyclic entities.

To illustrate, fluoride ion-mediated intramolecular conjugate additions could be realized from the Michael accepting precursors,[17] and so when the CM products **2** and **5** were treated with stoichiometric amounts of tetrabutylammonium fluoride in tetrahydrofuran at 0 °C, rapid conversions to the substituted cyclopentanes **21** and **22** occurred (Table 2).

Table 2. Preparation of Substituted Cyclopentanes[a]

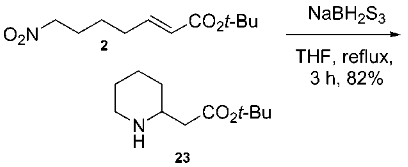


nitroalkene	cyclopentane	yield (%)
2	 **21**	91[a]
5	 **22**	90[b]

[a] Cis/trans = 1:7. [b] Trans isomer observed exclusively.

Furthermore, as illustrated in Scheme 3, we also observed that the facile reduction of nitroalkene **2** with the mild sulfurated sodium borohydride reagent[18] afforded the corresponding amine, which subsequently cyclized to give **23**.

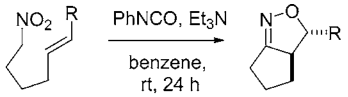
Scheme 3. Synthesis of Piperidine **23**

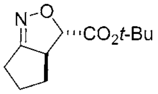
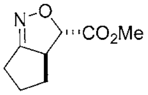
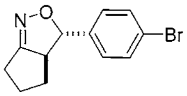


Intramolecular [3+2] nitrile oxide cycloaddition reactions were also carried out by treating the CM products **2**, **6**, and **10** with phenyl isocyanate and a catalytic amount of triethylamine in benzene according to the published procedure.[19] This afforded the highly desirable functionalized isoxazolines **24**−**26** (Table 3).

In conclusion, we report an efficient CM protocol to prepare functionalized aliphatic nitro compounds which are

Table 3. Preparation of Substitued Isoxazolines



nitroalkene	isoxazoline		yield (%)
2		**24**	90
6		**25**	88
10		**26**	91

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(16) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(17) Soengas, R. G.; Estévez, J. C.; Estévez, R. J.; Maestro, M. A. *Tetrahedron*: *Asymmetry* **2003**, *14*, 1653.

not commercially available, and would otherwise be difficult to access. These CM products have wide application as precursors for many transformations.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1**−**3** and **5**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070557K

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(18) (a) Lalancette, J. M., Jr.; Freche, A.; Birndle, J. R.; Laliberte, M. *Synthesis* **1972**, 527. (b) Lalancette, J. M., Jr.; Freche, A.; Montreux, R. *Can. J. Chem.* **1968**, *46*, 2754.

(19) (a) Yuan, C.; Li, C. *Tetrahedron Lett.* **1993**, *34*, 5959. (b) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826.