Cross Metathesis of *N*-Allylamines and α,β-Unsaturated Carbonyl Compounds: A One-Pot Synthesis of Substituted Pyrroles

Syed Shafi,[a] Mariusz Kędziorek,[b] Karol Grela*[a,b]

[a] Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

[b] Department of Chemistry, Warsaw University, Pasteura 1, 02-093 Warsaw, Poland
Fax +48(22)3432109; E-mail: klgrela@gmail.com

Received 9 October 2010

Abstract: A tandem reaction involving cross metathesis followed by concomitant cyclisation has been developed for the synthesis of substituted pyrroles. Various protected electron-deficient *N*-allylamines reacted with α,β-unsaturated carbonyl compounds in the presence of Lewis acids under the cross metathesis conditions using selected Ru olefin metathesis catalysts in order to form pyrroles.

Key words: ruthenium, catalysis, olefin metathesis, Lewis acids, heterocycles

In recent years, olefin metathesis has been regarded as one of the most important C=C bond-forming processes and has been utilized extensively in total syntheses.[1] The advent of well-defined catalyst systems (Figure 1) that combine excellent activity and broad functional group compatibility has been the major factor in popularizing this reaction.[2] The wealth of synthetic transformations that can be accomplished is astonishing, and there are countless applications of metathesis to form complex molecules. One of the most powerful tactics for the synthesis of carbocyclic and heterocyclic frameworks is ring-closing metathesis (RCM). Recently RCM has attracted some interest as a new tool for the synthesis of aromatic compounds.[3]

However, in the context of aromatic and heteroaromatic ring formation, rationally designed RCM strategies have only recently been highlighted in the literature.[4] Indeed, many early examples of the synthesis of aromatic compounds by RCM were viewed as unwanted side reactions.[5] Olefin cross metathesis (CM), on the other hand, has recently become recognised as a tool for the synthesis of aromatic and heteroaromatic compounds. Very recently, Donohoe demonstrated the synthesis of heteroaromatic compounds with respect to pyrroles and furanes using a two-step strategy involving a combination of cross metathesis followed by Lewis acid catalysed cyclization.[6] Catalytic olefin CM is a convenient route to functionalise olefins from simple alkene precursors and has gained a lot of interest due to its applications in the formation of versatile synthetic intermediates.[1d,e]

As the pyrrole system is prevalent in natural and synthetic biologically active compounds, we focussed our attention on the development of a novel and flexible approach to these heteroaromatic compounds. Although many reports are present in literature that describe the synthesis of pyrroles through RCM of diallyl amines,[4] and by other methods,[7,8] a novel and efficient synthetic method remains an attractive goal. As part of our ongoing project on the applications of cross metathesis in the synthesis of heterocyclic compounds, we report herein a straightforward method for the preparation of pyrroles using protected *N*-allylamines and α,β-unsaturated carbonyl compounds under cross metathesis conditions.[6]

Initial studies were focused on examining the feasibility of applying CM to various N-protected allylamines that could be used for the synthesis of some marine alkaloids. We have successfully performed the cross metathesis between *N*-tosyl-allylamine and *tert*-butylacrylate to form the expected product **3** (Scheme 1).[9] To our surprise, when the same reaction was performed with crotanaldehyde **4**, pyrrole **5** was formed along with the de-allylated product **6** and traces of 'homodimerised' product **7**, instead of the cross metathesis product. Intrigued by this unexpected observation, we decided to study this reaction in more detail. The CM reaction between *N*-tosyl allylamine and crotonaldehyde was chosen as a model reaction, and

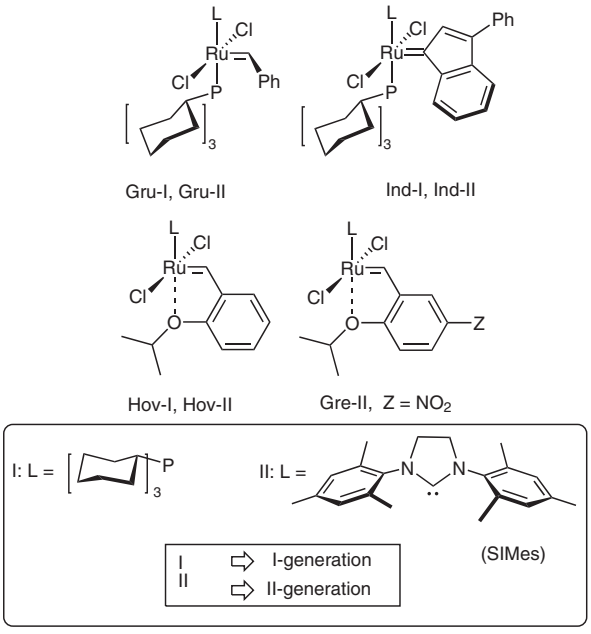
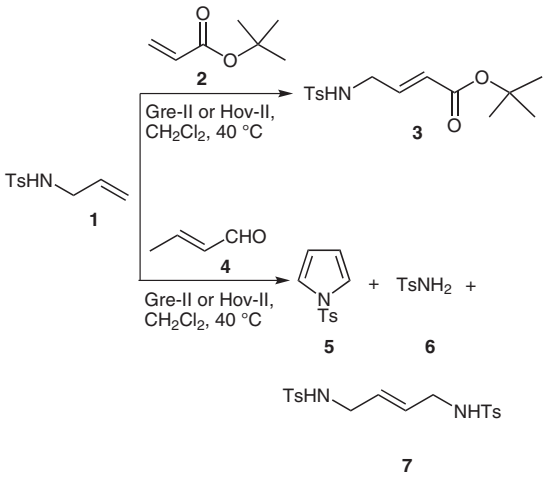


Figure 1 Selected ruthenium olefin metathesis pre-catalysts

SYNLETT 2011, No. 1, pp 0124–0128
Advanced online publication: 07.12.2010
DOI: 10.1055/s-0030-1259083; Art ID: G30810ST

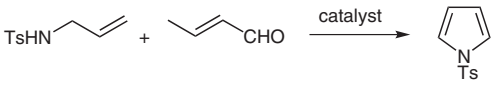


Scheme 1 Cross metathesis of *N*-tosyl allylamine **1**

a series of Grubbs-type Ru catalysts (Figure 1) were tested. This catalyst screening (Table 1) indicated that the model reaction did not work at all when **Gru-I** and **Gru-II** were employed at 40 °C in CH_2Cl_2; the de-allylated product **6** was found to be the major product in this case. When the reaction temperature was raised to 80 °C in toluene, only 5% of the pyrrole was isolated. Among the catalysts tested, the highly active carbene catalysts **Gre-II** and **Hov-II** gave pyrrole **5** in 32 and 65% yields, respectively. This transformation was repeated in different solvents (dichloroethane and toluene) at higher temperatures and with higher catalyst loading (20 mol%), however, the efficiency of the reaction did not improve. Under these conditions, the de-allylated product **6** was present in the reaction mixtures in all cases, which is probably due to the facile isomerization of allyl amine to enamines and coordination between the nitrogen and ruthenium.

It is known that Lewis acids can be used in such difficult cases to weaken the N···Ru coordination and inhibit the C–C double bond isomerisation.[9a] Therefore, the same model reaction was performed in the presence of various Lewis acids to examine the validity of this assumption. Interestingly, the pyrrole moiety was formed in moderate to high yields in the presence of various Lewis acids within significantly shorter reaction times (Table 2).

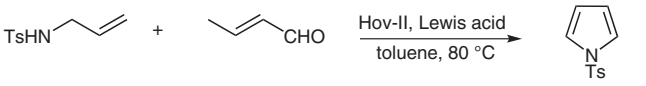
Table 1 Catalyst Screening for Cross Metathesis

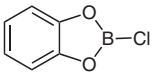


Catalyst	Catalyst (mol%)	Time (h)	Isolated yield (%)	
			CH_2Cl_2[a]	Toluene[b]
Gru-I	10	48	–	5
Gru-II	10	48	5	8
Ind-I	10	48	–	6
Ind-II	10	48	–	16
Gre-II	5	36	32	35
Hov-II	5	36	60	60

[a] Reaction temperature 40 °C.
[b] Reaction temperature 80 °C.

Table 2 Screening of Lewis Acids for the Cross Metathesis[a]



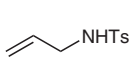
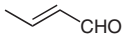
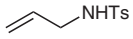
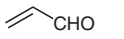
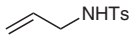
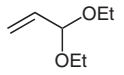
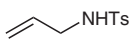
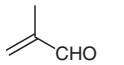
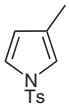
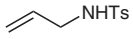
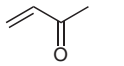
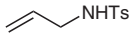
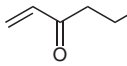
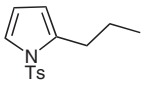
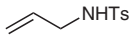
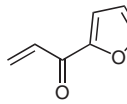
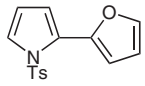
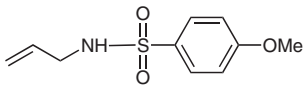
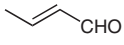
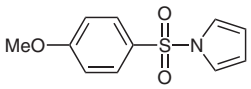
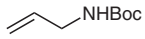
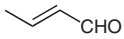
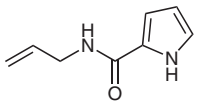
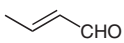
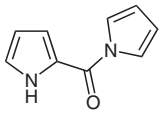
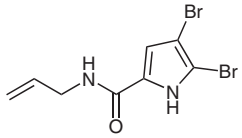
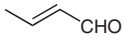
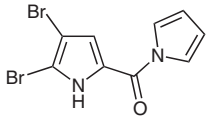
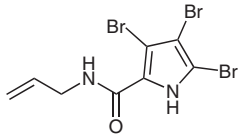
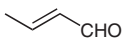
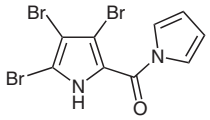
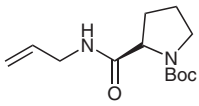
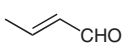
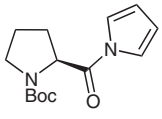
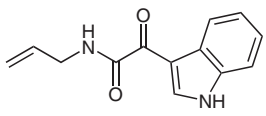
Lewis acid	Acid amount (mol%)	Time (min)	Yield (%)[b]
LiCl	100	120	5[c]
$AlCl_3$	100	120	5[c]
$Ti(Oi\text{-}Pr)_4$	100	120	20[c]
$Zn(OTf)_2$	100	60	60
$RuCl_3 \cdot nH_2O$	100	45	60
	100	90	60
$PhBCl_2$	100	90	70
$B(OPh)_3$	100	30	93
$B(OPh)_3$	50	30	93
$B(OPh)_3$	20	30	92
$B(OPh)_3$	10	30	92

[a] Reaction conditions: *N*-tosyl allylamine (0.47 mmol), crotonaldehyde (2.3 mmol), Lewis acid, **Hov-II** (5 mol%), toluene (5 mL).
[b] Isolated yields.
[c] Catalyst decomposed.

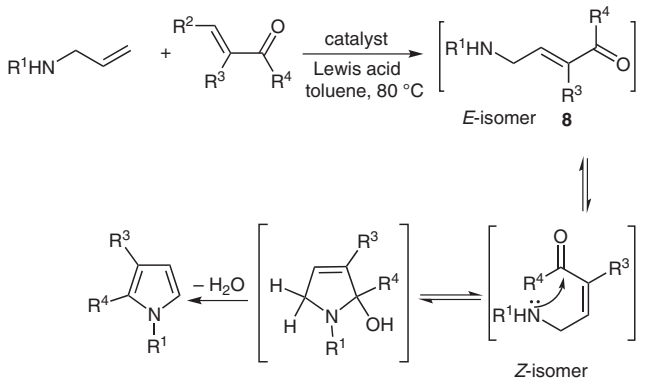
This study indicated that $B(OPh)_3$ is the best choice for this reaction. When the CM was run in the presence of one equivalent of $B(OPh)_3$, the reaction gave the pyrrole in 93% isolated yield in 30 minutes. Decreasing the amount of $B(OPh)_3$ did not affect the yield significantly. Even with a catalytic (10 mol%) amount of $B(OPh)_3$, the reaction afforded **5** in 92% yield within 30 minutes. $AlCl_3$, LiCl and $Ti(O^iPr)_4$ were too aggressive under these conditions, and they resulted in decomposition of the catalyst within a short time. From the above optimization trials, **Hov-II** and triphenyl borate were selected for further investigation. This new protocol was then successfully used in the synthesis of a set of substituted pyrrole derivatives from protected *N*-allylamines (Table 3).

The serendipitous formation of the pyrrole ring systems can be explained by the plausible mechanism shown in Scheme 2.[6] The cross metathesis takes place first, which leads in the formation of α,β-unsaturated carbonyl compound **8**, which (as the *Z*-isomer) undergoes immediate cyclization[10] and dehydration to form the pyrrole. The isomerisation/cyclisation step proceeds faster in the presence of Lewis acids. This proposal was further confirmed by a separate experiment, in which the CM reaction between **1** and acrolein diethyl acetal **9** was assessed

Table 3 Preperation of Substituted Pyrroles via CM[a]

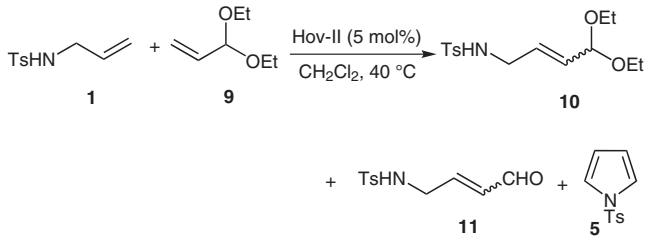
Entry	N-Protected allylamine (X)	CM partner (Y)	Product (Z)	Time (min)	Yield (%)[b]
1				30	92
2				30	90
3				30	60
4				45	70
5				45	60
6				45	54
7				60	30
8				30	91
9				45	60
10				75	60
11				75	60
12				90	43
13				50	57
14				90	15[c]

[a] Reagents and conditions: **Hov-II** (5 mol%), $B(OPh)_3$ (10 mol%), 80 °C, toluene.
[b] Isolated yield.
[c] 1,2-Dichloroethane was used as solvent.



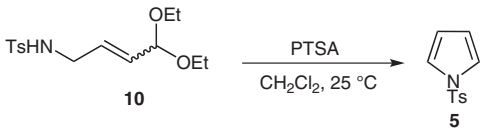
Scheme 2 Plausible mechanism of pyrrole ring formation

(Scheme 3). This reaction gave a mixture of products, including the expected cross metathesis product **10**, aldehyde **11** and pyrrole **5** in a 30:7:1 ratio. Compound **11** was difficult to isolate because it cyclised immediately.



Scheme 3 Cross metathesis between **1** and **9**

When pure isolated compound **10** was reacted with *p*-toluene sulfonic acid, compound **5** was formed within ten minutes (Scheme 4). This suggests that the reaction involved in pyrrole formation does indeed proceed through a highly reactive cross metathesis product i.e., an α,β-unsaturated carbonyl compound, which undergoes concomitant cyclisation to form the pyrrole under the reaction conditions.



Scheme 4 Deprotection of isolated acetal **10** leading to **5**

To assess the generality of this reaction, cross metathesis reactions between a range of substituted *N*-allylamines and various α,β-unsaturated carbonyl compounds were performed using 5 mol% **Hov-II** catalyst and 10 mol% $B(OPh)_3$ in toluene at 80 °C for 30–120 min; the results are summarized in Table 3.

We also noted that when the protecting groups of the allylamine partner were electron-withdrawing (Ts, Boc, etc.), the pyrroles were formed in moderate to high yields. However, allyl amines protected with electron-donating groups, such as *N*-benzyl, *N*-(1-methyl)benzyl, or *N*-(2,4,6-trimethyl)phenyl, did not lead to a productive reaction, probably due to the highly basic nature of the nitrogen atom. The same result (catalysts decomposition) was observed, when unprotected allylamine was used as the CM partner.

In conclusion, we have developed a new one-pot CM/cyclization protocol for construction of the pyrrole ring system, based on the reaction between electron-deficient *N*-allylamines and α,β-unsaturated aldehydes and ketones.[11–13] We expect that this reaction can find applications in the synthesis of various pyrrole-containing molecules.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

The authors thank the 'Kasa Mianowskiego' Foundation and the Foundation for Polish Science for the postdoctoral fellowship (for S.S.) and for a professorship 'Mistrz' (for K.G.).

References and Notes

(1) For reviews, see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490. (b) *Handbook of Metathesis*, Vol. 1-3; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, **2003**, 1234. (c) Furstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012. (d) Blechert, S.; Connon, S. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900. (e) Vernall, A. J.; Abell, A. D. *Aldrichimica Acta* **2003**, *36*, 93.

(2) (a) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 4035. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (c) Scholl, M.; Ding, S.; Choon, W. L.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (d) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791. (e) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.

(3) (a) Michaut, A.; Rodriguez, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 5740. (b) Martin, S. F.; Deiters, A. *Chem. Rev.* **2004**, *104*, 2199. (c) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. J. M. *Chem. Rev.* **2004**, *104*, 2239. (d) van Otterlo, W. A. L.; de Koning, C. B. *Chem. Rev.* **2009**, *109*, 3743. (e) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Chem. Eur. J.* **2008**, *14*, 5716.

(4) Donohoe, T. J.; Orr, A. J.; Bingham, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 2664; and references cited therein.

(5) (a) Bassindale, M. J.; Hamley, P.; Leitner, A.; Harrity, J. P. A. *Tetrahedron Lett.* **1999**, *40*, 3247. (b) Kinderman, S. S.; Doodeman, R.; van Beijma, J. W.; Russcher, J. C.; Tjen, K. C. M. F.; Kooistra, T. M.; Mohaselzadeh, H.; van Maarseveen, J. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *344*, 736.

(6) (a) During the preparation of this manuscript, a related two-step approach to substituted pyrroles via olefin cross metathesis and subsequent acid-catalysed cyclisation was published by Donohoe et al., presenting also an excellent example of the application of this methodology towards the synthesis of the tetrasubstituted pyrrole subunit of

Atorvastatin, see: Donohoe, T. J.; Race, N. J.; Bower, J. F.; Callens, C. K. A. *Org. Lett.* **2010**, *12*, 4094. (b) Donohoe, T. J.; Bower, J. F. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 3373. (c) Krische, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 3279.

(7) Poulard, C.; Cornet, J.; Legoupy, S.; Dujardin, G.; Dhal, R.; Huet, F. *Lett. Org. Chem.* **2009**, *6*, 359.

(8) Saito, A.; Konishi, T.; Hanzawa, Y. *Org. Lett.* **2010**, *12*, 372; and references cited therein.

(9) For selected examples of CM with allyl amines, see: (a) Vedrenne, E.; Dupont, H.; Sabrina, O.; Elkaïm, L.; Grimaud, L. *Synlett* **2005**, 670. (b) Dewi, P.; Blechert, S. *Eur. J. Org. Chem.* **2006**, 1852. (c) Gebauer, J.; Dewi, P.; Blechert, S. *Tetrahedron Lett.* **2005**, *46*, 43. (d) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(10) Paulus, O.; Alcaraz, G.; Vaultier, M. *Eur. J. Org. Chem.* **2002**, *14*, 2565.

(11) General procedure: All reactions were performed using Schlenk techniques under an argon atmosphere. Solvents were degassed (using Freeze–Pump–Thaw techniques) before use. Metathesis catalysts and all commercially available chemicals were used as received. See the Supporting Information for full experimental procedures and product characterisation data

(12) Pyrrol-1-yl(1*H*-pyrrol-2-yl)methanone (**10z**); Typical procedure: In a dry Schlenk tube, substrate **10x** (100 mg, 0.66 mmol), $B(OPh)_3$ (19 mg, 10 mol%) and crotonaldehyde (233 mg, 3.3 mmol) were dissolved in anhydrous toluene (5 mL) and stirred for 5 min under an argon atmosphere. The first portion of the catalyst **Hov-II** (10.5 mg, 2.5 mol%) was added as a solid. The reaction mixture was heated to reflux and, after 15 min, the second portion of the catalyst was added (10.5 mg, 2.5 mol%) under an argon atmosphere and heating was continued until the reaction was complete according to TLC. The reaction mixture was cooled and the solvent was evaporated. The crude product was purified by flash chromatography (*c*-hexane–EtOAc, 19:1) to yield **10z** as a colourless solid (64.01 mg, 60%); Mp 56–58 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.36 (t, *J* = 2.30, 2.29 Hz, 2 H), 6.37–6.38 (m, 1 H), 6.98–6.99 (m, 1 H), 7.11–7.14 (m, 1 H), 7.52 (t, *J* = 2.29, 2.30 Hz, 2 H), 9.86 (br, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 111.19, 112.71, 117.61, 120.65, 123.92, 124.95, 159.01. IR (KBr): 3306, 3158, 2958, 2924, 1645, 1545, 1467, 1456, 1424, 1412, 1389, 1345, 1277, 1244, 1138, 1108, 1099, 1074, 1042, 990, 941, 887, 864, 842, 766, 751, 728, 630, 604 cm^{-1}. MS (EI): *m*/*z* (%) = 160 (91) $[M]^{+\cdot}$, 94 (100), 67 (48), 66 (28). HRMS (EI): *m*/*z* calcd for $C_9H_8N_2O$: 160.06366; found: 160.06381. Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.44; H, 4.88; N, 17.57.

(13) This work was presented for the first time during the European Congress of Young Chemists 'YoungChem 2009', Warsaw, Poland, October 14–18, 2009: '*Ru catalyzed imine formation followed by RCM of N- allylamines*: *A tandem reaction towards the synthesis of substituted pyrroles*'; S. Shafi, oral presentation