ORGANIC LETTERS

2010
Vol. 12, No. 20
4658−4660

Asymmetric Allylic Alkylation in Combination with Ring-Closing Metathesis for the Preparation of Chiral N-Heterocycles

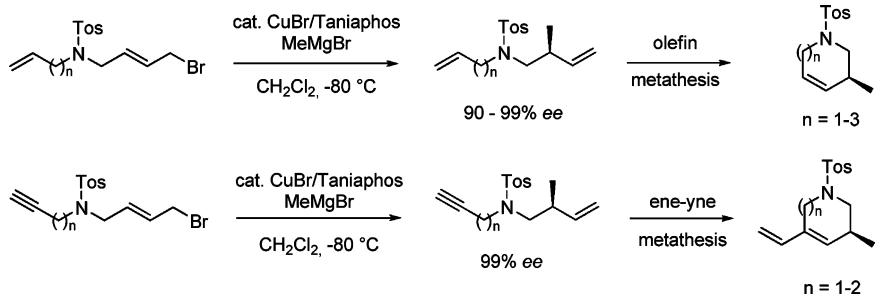
Johannes F. Teichert, Suyan Zhang, Anthoni W. van Zijl, Jan Willem Slaa, Adriaan J. Minnaard, and Ben L. Feringa*

Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands

b.l.feringa@rug.nl

Received August 17, 2010

ABSTRACT



Asymmetric copper-catalyzed allylic substitution with methylmagnesium bromide is employed in combination with ring-closing olefin metathesis or ene−yne metathesis to achieve the synthesis of chiral, unsaturated nitrogen heterocycles. The resulting six- to eight-membered chiral heterocycles are accessible in high yields and with excellent enantioselectivities.

Nitrogen-containing heterocycles are ubiquitous in naturally occurring compounds, such as alkaloids, but are also key structural features in many biologically active products.[1−4] Among these, nitrogen heterocycles with various ring sizes bearing stereogenic centers are frequently observed.[5−10] For example, poisonous frogs produce a variety of biologically active chiral piperidines featuring methyl substituents at the stereocenters.[11,12] These structures represent interesting targets for synthesis,[13−16] imposing particular challenges with regard to the construction of the stereogenic centers with high selectivity. One approach that has been frequently exploited is the use of ring-closing metathesis for the construction of *N*-heterocycles,[14,17−19] which has among

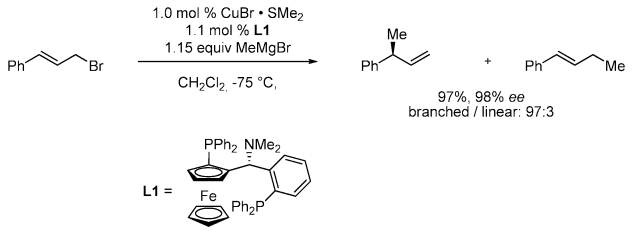
(1) Fattorusso, E.; Taglialatela-Scafati, O. *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*; Wiley-VCH: Weinheim, 2007.
(2) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603–626.
(3) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862–2892.
(4) Ohagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637–651.
(5) Boger, D. L.; Turnbull, P. *J. Org. Chem.* **1997**, *62*, 5849–5863.
(6) Martin, S. F.; Liao, Y. S.; Wong, Y. L.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691–694.
(7) Pilli, R. A.; de Oliveira, M. D. C. F. *Nat. Prod. Rep.* **2000**, *17*, 117–127.
(8) Sakai, R.; Higa, T. *J. Am. Chem. Soc.* **1986**, *108*, 6404–6405.
(9) Smith, A. B.; Cho, Y. S.; Pettit, G. R.; Hirschmann, R. *Tetrahedron* **2003**, *59*, 6991–7009.
(10) Wipf, P.; Spencer, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 225–235.
(11) Daly, J. W.; Noimai, N.; Kongkathip, B.; Kongkathip, N.; Wilham, J. M.; Garraffo, H. M.; Kaneko, T.; Spande, T. F.; Nimit, Y.; Nabhitabhata, J.; Chan-Ard, T. *Toxicon* **2004**, *44*, 805–815.
(12) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556–1575.
(13) Alibes, R.; Figueredo, M. *Eur. J. Org. Chem.* **2009**, 2421–2435.
(14) Arisawa, M.; Nishida, A.; Nakagawa, M. *J. Organomet. Chem.* **2006**, *691*, 5109–5121.
(15) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813.
(16) Naito, T. *Chem. Pharm. Bull.* **2008**, *56*, 1367–1383.
(17) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.

10.1021/ol101944j © 2010 American Chemical Society
Published on Web 09/23/2010

others been employed for the synthesis of non-natural amino acids.[20,21]

We have developed the asymmetric Cu-catalyzed allylic substitution of allylic bromides with Grignard reagents, employing chiral ferrocene-based bisphosphine ligands (Scheme 1).[22−26] This catalytic process is especially suited

Scheme 1. Cu-Catalyzed Allylic Alkylation of Cinnamyl Bromide

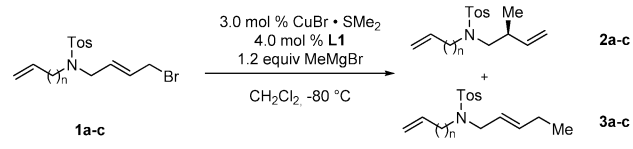


for the introduction of chiral methyl substituents, a structural motif frequently observed in naturally occurring compounds.[27] One major advantage of this methodology is that it furnishes terminal olefinic bonds, which represent ideal starting points for further modifications. This concept has been successfully applied in the synthesis of chiral allylic esters, which are important building blocks for the preparation of chiral lactones.[28] Similar approaches have been reported for the synthesis of chiral carbocycles by combination of allylic substitution followed by ring-closing metathesis.[29,30]

We anticipated that the Cu-catalyzed asymmetric allylic alkylation would serve as an ideal basis for the synthesis of nitrogen-containing heterocycles of various ring sizes, when combined with olefin or ene-yne ring-closing metathesis. When starting off from allylic bromides substituted with protected amine and terminal olefin or alkyne substituents, the obtained chiral products could subsequently be transformed to the correspoding unsaturated piperidines, azepanes or azocanes. One important feature of this approach is the fact that the resulting compounds bearing olefins or dienes are well-suited chiral building blocks for further modifications.

The *N*-substituted allylic bromides **1** and **5** (Tables 1 and 3) of various chain lengths are available in a few steps from commercially available compounds.[31]

Table 1. Asymmetric Allylic Alkylation of Allylic Bromides **1**



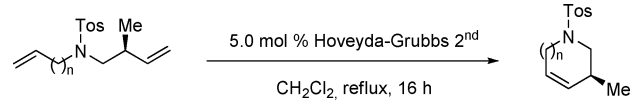
entry	*n*	branched (**2**)/linear (**3**)	yield (%) (for **2**)	ee (%)
1	1 (**1a**)	95:5	74 (**2a**)	99
2	2 (**1b**)	98:2	84 (**2b**)	90
3	3[a] (**1c**)	92:8	72 (**2c**)	98

[a] 6.00 mol % of CuBr•SMe_2 and 8.00 mol % of **L1** were used.

When allyl bromides **1** with terminal olefin substituents were subjected to allylic alkylation conditions (3.0 mol % of CuBr•SMe_2, 4.0 mol % of **L1** (Taniaphos[32−34]), 1.2 equiv of MeMgBr in CH_2Cl_2 at −80 °C), the desired chiral products **2** were obtained in good yields and up to excellent enantioselectivities (reaching 99% ee, Table 1, entry 1). Furthermore, the product distribution of branched (**2**) to linear (**3**) was very good, exceeding 92:8 favoring the branched products. To reach full conversion of **1c** ($n = 3$) (Table 1, entry 3), a higher catalyst loading of 6.0 mol % of CuBr•SMe_2 and 8.0 mol % of **L1** was required.

Chiral compounds **2** were subsequently transformed to the corresponding *N*-heterocycles **4** by ring-closing metathesis (Table 2). With 5.0 mol % of Hoveyda−Grubbs second-

Table 2. Ring-Closing Metathesis of Olefinic Substrates **2**



entry	*n*	yield (%)	ee (%)
1	1 (**2a**)	54 (**4a**)[36]	99
2	2 (**2b**)	61 (**4b**)	90
3	3 (**2c**)	77 (**4c**)	98

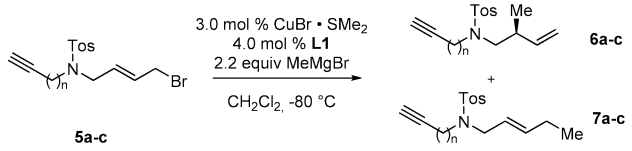
generation catalyst,[35] the six- to eight-membered rings were obtained in moderate to good yields. The best result was found for the eight-membered unsaturated azocane **4c** (77%,

(18) Felpin, F. X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693–3712.
(19) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieraugel, H. *Eur. J. Org. Chem.* **1999**, 959–968.
(20) Hassan, H. M. A.; Brown, F. K. *Chem. Commun.* , *46*, 3013–3015.
(21) Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677–680.
(22) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852.
(23) López, F.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2006**, 409–411.
(24) van Zijl, A. W.; López, F.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2007**, *72*, 2558–2563.
(25) van Zijl, A. W.; Szymanski, W.; López, F.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 6994–7002.
(26) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823.
(27) ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2010**, *46*, 2535–2547.
(28) Geurts, K.; Fletcher, S. P.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 15572–15573.
(29) Alexakis, A.; Croset, K. *Org. Lett.* **2002**, *4*, 4147–4149.
(30) Giacomina, F.; Riat, D.; Alexakis, A. *Org. Lett.* **2010**, *12*, 1156–1159.
(31) For the synthetic routes, see the Supporting Information.
(32) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 3212–3215.
(33) Fukuzawa, S.; Yamamoto, M.; Hosaka, M.; Kikuchi, S. *Eur. J. Org. Chem.* **2007**, 5540–5545.
(34) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 3666.
(35) Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760–3765.

Table 2 entry 3). It is important to note that the ee of the desired product was not compromised during the reaction.

For the synthesis of chiral *N*-heterocycles carrying a diene motif, the synthesis started from allylic bromides **5** bearing terminal alkyne substituents of various chain lengths. Under standard allylic substitution conditions, the desired chiral products **6** were isolated in good yields (Table 3). In all cases,

Table 3. Asymmetric Allylic Alkylation of Allylic Bromides **5**



entry	*n*	branched (**6**)/linear (**7**)	yield (%) for **6**	ee (%)
1	1 (**5a**)	95:5	77 (**6a**)	99
2	2 (**5b**)	96:4	53 (**6b**)[37]	99
3	3[a] (**5c**)	95:5	82 (**6c**)	99

[a] 6.00 mol % of $CuBr{\cdot}SMe_2$ and 8.00 mol % of **L1** were used.

excellent regio- and enantioselectivities were achieved (**6**/**7** >95:5, 99% ee). As in the case of the olefinic substrates **1** (Table 1), the longest spacer length (**5c**, $n = 3$) required a slightly higher catalyst loading to achieve full conversion (Table 3, entry 3).

For the ene−yne metathesis of compounds **6** to reach full conversion, 5.0 mol % Grubbs first generation catalyst under an ethene atmosphere was employed. The influence of ethene was found to be essential for the reaction to proceed to **8**.[38,39] The resulting six- and seven-membered nitrogen-containing rings with diene motifs **8a**,**b** were isolated in good yields (Table 4). Again, no loss of ee was observed in this transformation, making this a viable pathway for the construction of chiral nitrogen-containing heterocycles with various ring sizes.

The reaction of **6c** under the given conditions did not produce the desired eight-membered ring. The ene-yne

(36) Reaction reaches full conversion; one unidentified side product is present in the reaction mixture.

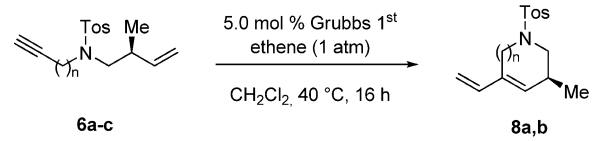
(37) Reaction reaches 75% conversion; no side products were observed.

(38) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082–6083.

(39) In the absence of an ethene atmosphere, no turnover was observed.

(40) Reaction reaches 90% conversion; one unidentified side product observed.

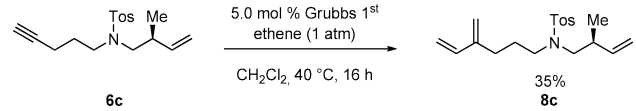
Table 4. Ene−Yne Metathesis of Alkyne Substrates **6**



entry	*n*	yield (%)	ee (%)
1	1 (**6a**)	77 (**8a**)	99
2	2 (**6b**)	65 (**8b**)[40]	99
3	3 (**6c**)	n.d.	n.d.

metathesis proceeded to the linear product **8c** in moderate yields (Scheme 2), where the alkyne moiety of **6c** reacted

Scheme 2. Ene−Yne Metathesis of **6c**



in an intermolecular fashion with ethene instead of intramolecularly with the terminal olefin. Product **8c** in turn did not react any further to the desired ring system under the reaction conditions.[41]

In summary, we have demonstrated that chiral unsaturated heterocycles are available in excellent enantiomeric excess and good yields via a combination of Cu-catalyzed allylic substitution and Ru-catalyzed ring-closing metathesis. Six- to eight-membered nitrogen-containing rings are easily available through this short synthetic pathway. By employing terminal olefins, singly unsaturated rings are accessible while terminal alkynes were transformed to the corresponding dienes in good yields and 99% ee. The obtained compounds are ideal chiral building blocks for further functionalization through the olefinic bonds.

Supporting Information Available: Experimental procedures and spectroscopic data for the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101944J

(41) For optimization results, see the Supporting Information.