ORGANIC LETTERS

2007
Vol. 9, No. 22
4463−4466

Regiodivergent Metal-Catalyzed Rearrangement of 3-Iminocyclopropenes into N-Fused Heterocycles

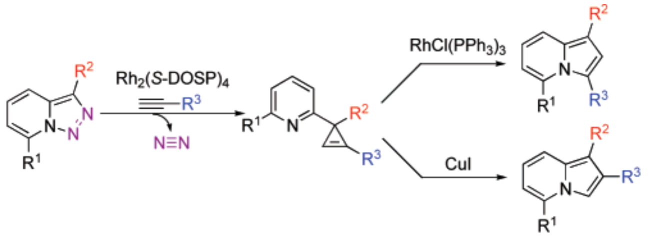
Stepan Chuprakov and Vladimir Gevorgyan*

*Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street,
Room 4500, Chicago, Illinois 60607*

vlad@uic.edu

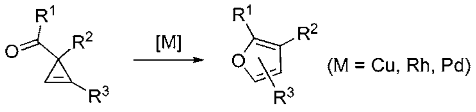
Received July 31, 2007

ABSTRACT

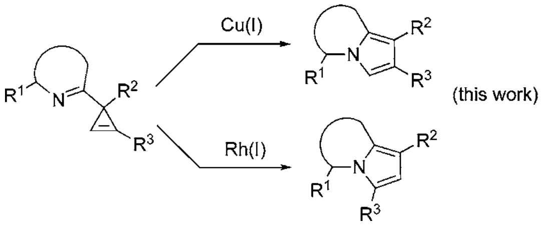


A highly efficient regiodivergent method for the synthesis of N-fused heterocycles via transition-metal-catalyzed rearrangement of 3-iminocyclopropenes has been developed.

Transition-metal-catalyzed chemistry of cyclopropenes[1] benefits from their enormous ring strain.[2] The highly reactive double bond enjoys a variety of addition[3] and cycloaddition[4] reactions,[5] while rearrangements allow for construction of various carbo-[6] and heterocycles.[6c−g,7] Thus, there are several reports on the metal-catalyzed rearrangements of 3-acylcyclopropenes into furans (eq 1).[6c−g,7] However, to the best of our knowledge, an analogous metal-catalyzed construction of N-containing heterocycles has no precedents.[8] Herein, we wish to report the first example of a regiodivergent Cu- and Rh-catalyzed rearrangement of 3-iminocyclopropenes into N-fused pyrroles, heterocyclic scaffolds endowed with a wide array of important biological properties (eq 2).[9]



(1)



(2)

It deserves mentioning that, until recently, there were no convenient approaches toward C-3 imino-substituted cyclopropenes, potentially useful building blocks for organic chemistry.[1] Recently, we found[10] that 7-halo-substituted N-fused triazoles **1** could be used as surrogates for α-imino

---

(1) For recent reviews, see: (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221. (c) Fox, J. M.; Yan, N. *Curr. Org. Chem.* **2005**, *9*, 719.

(2) For discussion on the strain energy in small rings, see, for example: Back, R. D.; Dmitrenko, O. *J. Am. Chem. Soc.* **2004**, *126*, 4444.

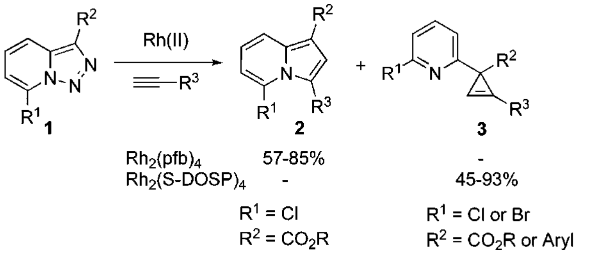
(3) For carbometalations, see: (a) Liao, L.; Fox, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 14322. (b) Liu, X.; Fox, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 5600. For hydrometalations, see: (c) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2002**, *124*, 11566. (d) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198. (e) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2004**, *126*, 3688.

(4) For selected examples, see: (a) Diev, V. V.; Kostikov, R. R.; Gleiter, R.; Molchanov, A. P. *J. Org. Chem.* **2006**, *71*, 4066. (b) Ma, S.; Zhang, J.; Lu, L.; Jin, X.; Cai, Y.; Hou, H. *Chem. Commun.* **2005**, 909. (c) Palleria, M. K.; Fox, J. M. *Org. Lett.* **2005**, *7*, 3593. (d) Weatherhead-Kloster, R. A.; Corey, E. J. *Org. Lett.* **2006**, *8*, 171. (e) Padwa, A.; Kulkarni, Y. S.; Terry, L. W. *J. Org. Chem.* **1990**, *55*, 2478.

(5) For coupling reactions, see: (a) Yin, J.; Chisholm, J. D. *Chem. Commun.* **2006**, 632. (b) Chuprakov, S.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 3714.

10.1021/ol702084f CCC: $37.00

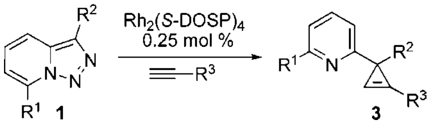
diazocompounds[11] in the Rh(II)-catalyzed chemoselective reaction with terminal alkynes to produce indolizines **2** or 3-(2-pyridyl)cyclopropenes **3**, depending upon catalyst source (eq 3).[10] The presence of the halogen substituent in **1** was crucial, as no reaction occurred with triazoles possessing H or alkyl groups at C-7.[10] Although the direct Rh(II) perfluorobutyrate-catalyzed transannulation of triazoles provided a rapid and convenient approach toward indolizines,[10] it was not without limitations. Thus, only triazoles that possessed strong electron-withdrawing group at C-3 ($R^2 = CO_2R$) were efficient in this transannulation reaction. We hypothesized that, potentially, the rearrangement of 3-(2-pyridyl)cyclopropenes **3** could provide alternative routes to indolizines **2** as shown in eq 2.



(3)

To this end, we tested the generality of the Rh_2(S-DOSP)$_2$-catalyzed cyclopropenation of triazoles with alkynes. To our delight, we found that a variety of pyridyl-containing cyclopropenes can easily be synthesized in good yields via this method (Table 1).[12] Thus, triazoles **1a**−**d** possessing both electron-rich and electron-deficient aryl substituents at C-3 reacted smoothly with various alkyl-, aryl-, and alkenyl-containing alkynes to afford corresponding cyclopropenes **3** chemoselectively (Table 1). Cyclopropenation of 3-carbomethoxytriazole **1e** proceeded uneventfully, producing corresponding cyclopropenes **3** in good to excellent yields (entries 9−12, 14).

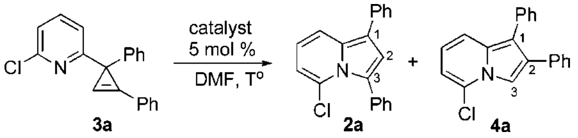
Table 1. Rh_2(S-DOSP)$_4$-Catalyzed Cyclopropenation of Pyridotriazoles with Alkynes



no.	R^1	R^2		R^3		yield,[a] %
1	Cl	Ph	**1a**	Ph	**3a**	81
2	Cl	Ph	**1a**	*p*-$OMeC_6H_4$	**3b**	79
3	Cl	Ph	**1a**	*p*-$CO_2MeC_6H_4$	**3c**	65
4	Br	Ph	**1b**	Ph	**3d**	88[b]
5	Cl	*p*-$OMeC_6H_4$	**1c**	Ph	**3e**	67
6	Cl	*p*-$OMeC_6H_4$	**1c**	*o*-tolyl	**3f**	45
7	Cl	*p*-$CF_3C_6H_4$	**1d**	Ph	**3g**	68
8	Cl	*p*-$CF_3C_6H_4$	**1d**	1-cyclohexenyl	**3h**	93
9	Cl	CO_2Me	**1e**	*p*-tolyl	**3i**	93[c]
10	Cl	CO_2Me	**1e**	*p*-$OMeC_6H_4$	**3j**	67
11	Cl	CO_2Me	**1e**	*p*-$CO_2MeC_6H_4$	**3k**	72
12	Cl	CO_2Me	**1e**	*m*-$CO_2MeC_6H_4$	**3l**	87
13	Br	Ph	**1b**	*n*-butyl	**3m**	69
14	Cl	CO_2Me	**1e**	Ph	**3n**	86[d]
15	Cl	Ph	**1a**	$(CH_2)_3Cl$	**3o**	68

[a] Isolated yield. [b] 8% ee. [c] 86% ee. [d] 84% ee.

Table 2. Metal-Catalyzed Rearrangement of Cyclopropene **3a**



no.	catalyst	*T* (°C)	**2a**:**4a** ratio[a]	yield,[b] %
1	$PdCl_2$	rt	2:1	23
2	$PtCl_2$	rt	4:1	38
3	$Pt(PPh_3)_4$	60	5:1	86
4	$NiCl_2$	60		0[c]
5	$RuCl_2(PPh_3)_3$	60	8:1	32
6	[Ir(cod)py(PCy_3)]PF_6	60	>99:1	49
7	**$RhCl(PPh_3)_3$**	**rt**	**>99:1**	**92**
8	$Rh_2(pfb)_4$	rt[d]	<1:99	31
9	$AgSbF_6$	60		0[c]
10	$AuCl_3$	60[d]		0[c]
11	**CuI**	**rt**	**<1:99**	**78**

[a] NMR ratio. [b] Combined NMR yield of both isomers. [c] A mixture of unidentified products formed. [d] Dichloroethane used as solvent.

Naturally, having in hand this convenient method for the synthesis of 3-iminocyclopropenes, we evaluated our hypothesis on the cyclopropene into N-fused pyrrole transformation (eq 2). To this end, we tested rearrangement of cyclopropene **3a** into indolizines **2a** and **4a** in the presence of a series of transition-metal catalysts (Table 2). The employment of Pd(II) and Pt(II) chlorides in DMF at room temperature resulted in low yields and moderate regioselectivity of rearrangement (entries 1 and 2). The yield was improved upon switching to Pt(0) complex (entry 3); however, the selectivity remained unsatisfactory. Gratify-

---

(6) (a) Padwa, A.; Blacklock, T.; Loza, R. *J. Am. Chem. Soc.* **1981**, *103*, 2404. (b) Padwa, A.; Blackbock, T. J.; Loza, R. *J. Org. Chem.* **1982**, *47*, 3712. (c) Müller, P.; Pautex, N.; Doyle, M. P.; Baheri, V. *Helv. Chim. Acta* **1990**, *73*, 1233. (d) Cho, S. H.; Liebeskind, L. S. *J. Org. Chem.* **1987**, *52*, 2631. (e) Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1997**, *62*, 1642. (f) Müller, P.; Gränicher, C. *Helv. Chim. Acta* **1993**, *76*, 521. (g) Müller, P.; Gränicher, C. *Helv. Chim. Acta* **1995**, *78*, 129.

(7) (a) Tomilov, Y. V.; Shapiro, E. A.; Protopopova, M. N.; Ioffe, A. I.; Dolgii, I. E.; Nefedov, O. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 631. (b) Davies, H. M. L.; Romines, K. R. *Tetrahedron* **1988**, *44*, 3343. (c) Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1991**, *56*, 6971. (d) Ma, S.; Zhang, J. *J. Am. Chem. Soc.* **2003**, *125*, 12386.

(8) For photochemical isomerization, see: Zimmerman, H. E.; Wright, C. W. *J. Am. Chem. Soc.* **1992**, *114*, 6603.

(9) For selected examples on biological activity of indolizines, see: (a) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. *J. Med. Chem.* **1996**, *39*, 3636. (b) Gundersen, L.-L.; Malterud, K. E.; Negussie, A. H.; Rise, F.; Teklu, S.; Østby, O. B. *Bioorg. Med. Chem.* **2003**, *11*, 5409.

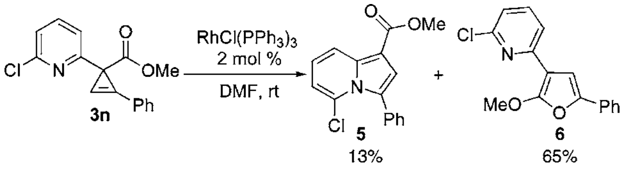
(10) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757.

(11) For cyclopropanation with 2-pyridyl diazo compounds, see: Davies, H. M. L.; Townsend, R. J. *J. Org. Chem.* **2001**, *66*, 6595.

(12) Despite the efficiency of Rh_2(S-DOSP)$_4$ in enantioselective cyclopropenations,[13] we observed very low levels of enantioselectivity in synthesis of 3-aryl-substituted cyclopropenes. However, selected examples indicate highly enantioselective cyclopropenation in a case of 3-carbomethoxy derivatives (see Table 1).

ingly, we found that the employment of Ir(I) and Rh(I) complexes led to the highly regioselective isomerization of **3a** into **2a** (entries 6 and 7) in moderate and excellent yields, respectively. Interestingly, when Rh(II) perfluorobutyrate was used as a catalyst, another regioisomer **4a**, with the substituent at C-2 position,[14,15] was formed as a single product, though in low yield (entry 8). AgSbF$_6$ and Au(III) chloride[16] were completely inefficient catalysts for this transformation (entries 9 and 10). However, Cu(I) iodide smoothly isomerized **3a** into indolizine **4a** in good yield and excellent regioselectivity (entry 11, Table 2).

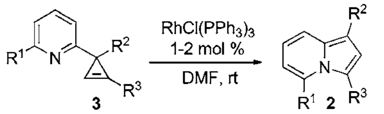
Next, we explored the scope of this novel regiodivergent rearrangement methodology. First, rearrangement of a series of 3-(2-pyridyl)cyclopropenes into 1,3-disubstituted indolizines **2** was tested under Rh(I) catalysis (Table 3). It was found that cyclopropenes possessing both electron-rich and electron-deficient aryl groups[17] at position C-3 and at the double bond underwent clean and regioselective rearrangement into indolizines **2**. Notably, 1-alkenyl- (entry 8) and Br-containing (entry 4) substrates were found to be equally efficient in this reaction, as well. Thus, the Rh(I)-catalyzed isomerization of cyclopropenes compliments the direct transannulation protocol,[10] providing access to a wider selection of 1,3-substituted indolizines possessing not only ester but also various aryl groups at C-3. Attempts to perform the analogous transformation with 3-carbomethoxycyclopropene **3n** produced only a small amount of the corresponding indolizine **5** together with furan **6** as major product of this reaction (eq 4). Formation of furan **6** in the presence of Wilkinson's catalyst is consistent with earlier observations (eq 1).[6c−g,7]

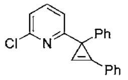
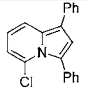
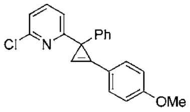
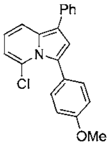
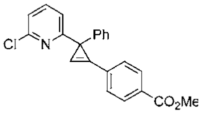
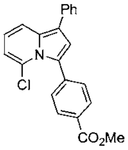
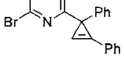
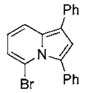
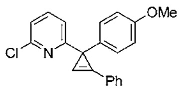
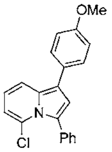
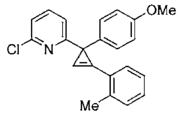
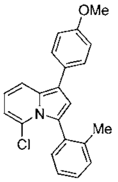
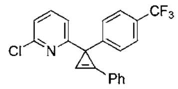
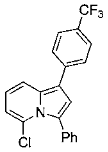
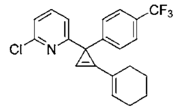
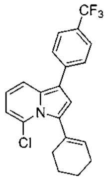


(4)

After successful synthesis of 1,3-disubstituted indolizines **2** (Table 3), we turned our attention to regioselective formation of valuble[14,15] 1,2-subsituted N-fused pyrroles **4** via the Cu(I)-catalyzed rearrangement. To our delight, a variety of 3-carbomethoxy- and 3-arylcyclopropenes reacted smoothly to produce indolizines **4** in good to excellent yields (Table 4). Electron-rich (entries 2 and 3) and electron-deficient (entries 4 and 5) aryl groups and alkyl substituents (entries 7 and 8) at the double bond of cyclopropene were equally well tolerated in this reaction. Gratifyingly, this rearrangement mode worked well with different 3-heteroaryl-cyclopropenes, such as oxazole[18] and isoquinoline[19] derivatives **3p** and **3r**, giving access to their fused analogues **4j** and **4k** in good yields (entries 10 and 11).

Table 3. Rh(I)-Catalyzed Rearrangement of Cyclopropenes



no.	cyclopropene 3		product 2		yield[a], %
1		**3a**		**2a**	85
2		**3b**		**2b**	91
3		**3c**		**2c**	79
4		**3d**		**2d**	87
5		**3e**		**2e**	81
6		**3f**		**2f**	93
7		**3g**		**2g**	84
8		**3h**		**2h**	88

[a] Isolated yield.

We propose the following mechanistic rationale for the novel regiodivergent rearrangement of imino cyclopropenes **3** into fused pyrroloheterocycles **2** and **4** (Scheme 1). Cyclopropene **3**, in the presence of Rh(I) complex, undergoes ring opening to produce the most substituted carbenoid **5**.[6c−e,7c] A nucleophilic attack by nitrogen lone pair on

---

(13) Davies, H. M. L.; Lee, G. H. *Org. Lett.* **2004**, *6*, 1233.

(14) The C-2 site of indolizine is unfunctionalizable position and a substituent must be introduced prior to cyclization (see ref 15).

(15) For a review, see: (a) Behnisch, R.; Behnisch, P.; Eggenweiler, M.; Wallenhorst, T. In *Houben-Weyl*; Kreher, R. P., Ed.; Georg Thieme Verlag Stuttgart: New York, 1994; Vol.E6a/2a, pp 323−451. See also: (b) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050.

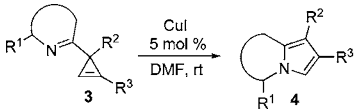
(16) For recent review on gold catalysis, see: Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180.

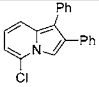
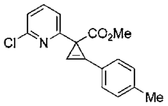
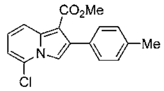
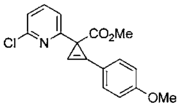
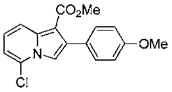
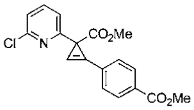
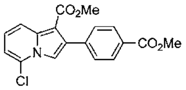
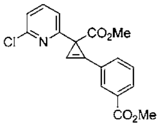
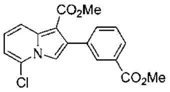
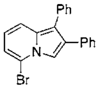
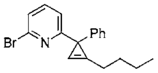
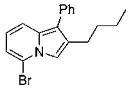
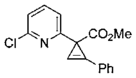
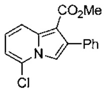
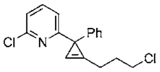
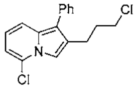
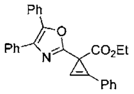
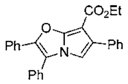
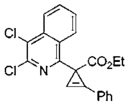
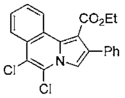
(17) Substrates, possessing alkyl substituents at C-1 position of cyclopropene ring produced only trace amounts of products under these reaction conditions.

(18) For the synthesis of oxazolyl diazo compound, see ref 11.

(19) Prepared via cyclopropenation of corresponding triazoloisoquinoline analogously to pyridyl derivatives **3a−o** (see the Supporting Information for details).

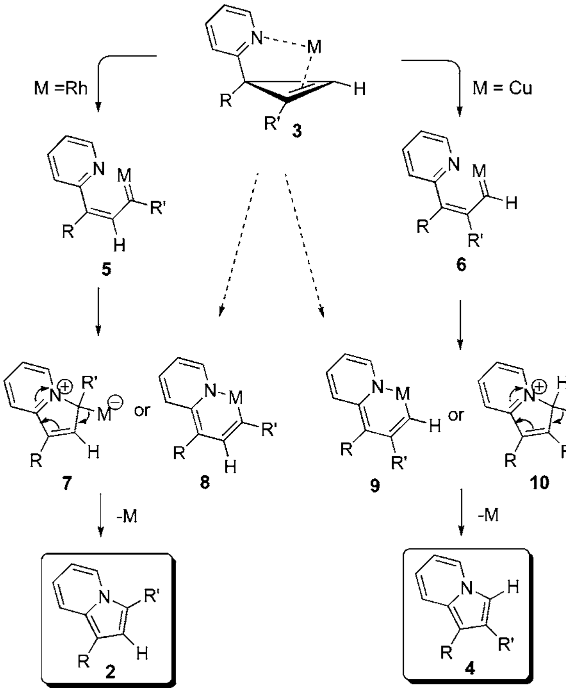
Table 4. Cu(I)-Catalyzed Rearrangement of Cyclopropenes



no.	cyclopropene 3		product 4		yield[a], %
1	**3a**			**4a**	75
2		**3i**		**4b**	83
3		**3j**		**4c**	95
4		**3k**		**4d**	73
5		**3l**		**4e**	81
6	**3d**			**4f**	78
7		**3m**		**4g**	71
8		**3n**		**4h**	67
9		**3o**		**4i**	73
10		**3p**		**4j**	71
11		**3r**		**4k**	88

[a] Isolated yield.

Scheme 1. Mechanistic Rationale for Regiodivergent Rearrangement Reactions



carbenoid center leads to the formation of zwitterion **7**. A subsequent elimination of the metal furnishes regioisomer **2**. In contrast, when Cu(I) catalyst is used, formation of less substituted carbenoid **6** occurs,[6c,f,g,7a] cyclization of which via a zwitterion **10** leads to the product **4** selectively. Alternatively, regioisomers **2** and **4** may arise via a reductive elimination of aza metalacycles **8** and **9**, respectively, which in turn are formed via a 6π-electrocyclization[6e,20] of carbenoids **5** and **6**, or directly from cyclopropene **3**, upon regioselective oxidative addition of the metal.[6e,7c] It was also proposed that isomeric carbenoids **5** and **6** could interconvert through the cycloaddition/cycloreversion equilibrium.[6d,e] We evaluated a possibility of such equilibrium by performing a crossover experiment in the presence of 5 equiv of "external" alkyne. However, no crossover products were detected, thus suggesting independent routes for the formation of **5** and **6**.

In summary, we have developed a highly efficient synthesis of 1,3- and 1,2-disubstituted N-fused pyrroloheterocycles,[9,21] including indolizines, pyrrolooxazole, and pyrroloisoquinoline, via a novel regiodivergent transition-metal-catalyzed rearrangement of 3-iminocyclopropenes. We also demonstrated that the latter can conviniently be synthesized from 1,2,3-triazoles.[23]

Acknowledgment. The support of the National Institutes of Health (GM-64444) and the National Science Foundation (CHE-0710749) is gratefully acknowledged.

Supporting Information Available: Preparative procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702084F

---

[20] Hoye, T. R.; Dinsmore, C. J.; Johnson, D. S.; Korkowski, P. F. *J. Org. Chem.* **1990**, *55*, 4518.

[21] Heterocyclic halides may be further functionalized via cross-coupling reactions.[22] We have also shown (see ref 10) that halogen can be efficiently removed from the products.

[22] For a review, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

[23] Halogen-free 3-(2-pyridyl)cyclopropenes were not examined in the described rearrangements as they were not available via cyclopropenation of pyridotriazoles (see ref 10).