ORGANIC LETTERS

2005
Vol. 7, No. 2
219−221

Copper-Catalyzed Anti-Stereocontrolled Ring-Opening of Azabicyclic Alkenes with Grignard Reagents

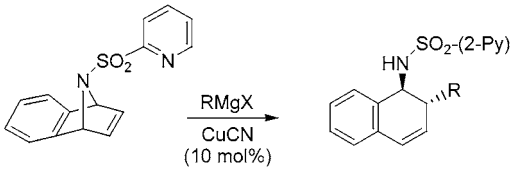
Ramón Gómez Arrayás,* Silvia Cabrera, and Juan C. Carretero*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

juancarlos.carretero@uam.es; ramon.gomez@uam.es

Received October 25, 2004

ABSTRACT



The anti-stereocontrolled alkylative ring-opening reaction of azabicyclic alkenes is reported. *N*-(2-Pyridyl)sulfonyl azabenzonorbornadiene reacts with Grignard reagents in the presence of catalytic amounts of CuCN to afford, in good yields and excellent anti selectivity, the corresponding dihydronaphthalene-1-amines.

The transition metal-catalyzed ring-opening reaction of heterobicyclic alkenes with nucleophiles is a powerful carbon−carbon bond-forming method for the rapid construction of stereochemically complex carbocyclic compounds.[1] Pioneering work in this area, including the development of asymmetric variants, as well as the exploration of its synthetic potential in natural product synthesis, has been reported by Lautens et al.[1,2]

In contrast to the widely studied ring-opening of oxa-bridged bicyclic alkenes,[1,3] there are few reports on stereocontrolled ring-opening reactions of their azabicyclic analogues,[2d,3b,4,5] although the resulting 1-aminodihydronaphthalenes are useful scaffolds for the preparation of potentially bioactive compounds. On the other hand, it must be noted that all precedents regarding the ring-opening addition of carbon-based nucleophiles to azabicycles are described to occur with syn stereoselectivity, resulting from *exo* attack on the azabicyclic unit. These examples include the enantioselective Pd-catalyzed addition of arylboronic acids and dimethylzinc to azabenzonorbornadienes, reported by Lautens et al.,[4] and the Pd- or Ni-catalyzed ring opening of azabenzonorbornadienes with organic halides or terminal acetylenes, described by Cheng et al.[5,6] To the best of our knowledge, the only precedent of anti-stereocontrolled opening of an azabicyclic alkene is the Rh-catalyzed reaction with nitrogen nucleophiles.[2d] Recently, we have described the anti-stereocontrolled copper-catalyzed alkylative ring-opening reaction of benzo- and alkyl-substituted oxabicyclic alkenes using Grignard reagents as widely available and versatile nucleophiles.[7,8] Herein, we report the extension of this method to the ring-opening reaction of the less reactive aza substrates by means of using the (2-pyridyl)sulfonyl group as the key

(1) For reviews, see: (a) Lautens, M. *Synthesis* **1993**, 177−185. (b) Chiu, P.; Lautens, M. *Top. Curr. Chem*. **1997**, *190*, 1−85. (c) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res*. **2003**, *36*, 48−58.

(2) For natural product synthesis, see: (a) Lautens, M.; Rovis, T. *J. Org. Chem*. **1997**, *62*, 5246−5247. (b) Lautens, M.; Rovis, T. *Tetrahedron* **1999**, 8967−8976. (c) Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett*. **2002**, *4*, 1879−1882. (d) Lautens, M.; Fagnou, K.; Zunic, V. *Org. Lett*. **2002**, *4*, 3465−3468.

(3) For recent examples, see: (a) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc*. **2004**, *126*, 1437−1447. (b) Cabrera, S.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed*. **2004**, *43*, 3944−3947. (c) Lautens, M.; Fagnou, K. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5455−5460. (d) Li, M.; Yan, X.-X.; Hong, W.; Zhu, X.-Z.; Cao, B.-X.; Sun, J.; Hou, X.-L. *Org. Lett*. **2004**, *6*, 2833−2835. (e) Leong, P.; Lautens, M. *J. Org. Chem*. **2004**, *69*, 2194−2196. (f) Dotta, P.; Kumar, P. G. A.; Pregosin, P. S. *Organometallics* **2004**, *23*, 2295−2304.

(4) (a) Lautens, M.; Hiebert, S.; Renaud, J.-L. *Org. Lett*. **2000**, *2*, 1971−1973. (b) Lautens, M.; Dockendorff, C. *Org. Lett*. **2003**, *5*, 3695−3698.

(5) (a) Duan, J.-P.; Cheng, C.-H. *Organometallics* **1995**, *14*, 1608−1618. (b) Feng, C.-C.; Nandi, M.; Sambaiah, T.; Cheng, C.-H. *J. Org. Chem*. **1999**, *64*, 3538−3543. (c) Rayabarapu, D. K.; Chiou, C.-F.; Cheng, C.-H. *Org. Lett*. **2002**, *4*, 1679−1682.

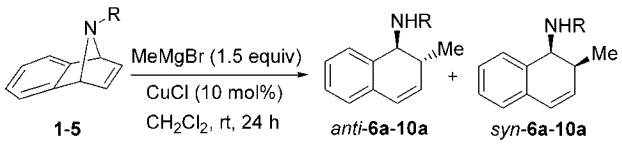
(6) For the asymmetric reductive ring-opening of aza-benzonorbornadienes, see: Li, L.-P.; Rayabarapu, D. K.; Nandi, M.; Cheng, C.-H. *Org. Lett*. **2003**, *5*, 1621−1624.

10.1021/ol0478133 CCC: $30.25
Published on Web 12/24/2004

activating group at the nitrogen atom.[9] This protocol constitutes the first anti-stereocontrolled procedure of alkylative ring opening of azabicyclic alkenes.

The starting point of our research was to define the appropriate protecting functionality at nitrogen and to identify the optimal reaction conditions. To improve the leaving group ability at nitrogen, we focused our attention on the carbamate **1** and, especially, the sulfonamides **2**−**5** (Table 1). The

Table 1. Screening of Different Activating Groups at Nitrogen for the Ring-Opening Reaction of Azabenzonorbornadiene



1-5 *anti*-**6a-10a** *syn*-**6a-10a**

entry	R group	substitution	conversion (%)[a]	product	anti/syn[a]
1	Boc	**1**	0	**6a**	
2	Ts	**2**	20	**7a**	71:29
3	(2-thiophene)sulfonyl	**3**	20	**8a**	62:38
4	(2-pyridyl)sulfonyl	**4**	85	**9a**	90:10
5	*p*-nosyl	**5**	b	**10a**	

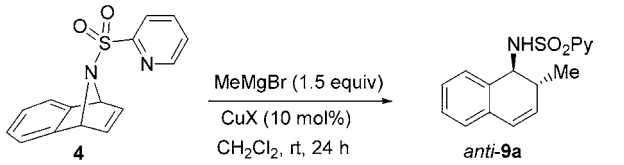
[a] Determined by ^{1}H NMR analysis of the crude reaction mixture (the remaining product is starting material). [b] Only decomposition products, together with starting material, were detected.

known sulfonamides **2** and **5** were synthesized by straightforward deprotection of carbamate **1** (TMSI/Et_3N), followed by treatment with the corresponding sulfonyl chloride.[2d] On the other hand, the heteroaryl sulfonamides **3** and **4** were readily prepared in good yields by direct Diels−Alder cycloaddition between benzyne, generated in situ from anthranilic acid and isoamyl nitrite, and the corresponding *N*-pyrrole derivative.

As shown in Table 1, the outcome of the ring-opening reaction of **1**−**5** with MeMgBr (CH_2Cl_2,[10] rt) in the presence of 10 mol % CuCl[11] proved to be quite dependent on the nature of the substitution at nitrogen. Thus, while no reaction was observed in the case of the *N*-Boc carbamate **1** after 24 h, the starting material being recovered unaltered (entry 1), the sulfonamides **2** and **3** provided the ring-opened products, albeit both the reactivity and the stereoselectivity were very low[12] (entries 2 and 3). On the other hand, the highly electrophilic *N*-*p*-nosyl derivative **5** led to a sluggish reaction, affording mainly decomposition products (entry 5). By far, the best results were obtained from the (2-pyridyl)sulfonyl derivative **4** (entry 4). Not only did this substrate show a remarkable reactivity, but also the reaction occurred with good anti stereocontrol.

Having established the optimal protecting group for the azabicyclic system, the effect of several commercially available copper salts on the ring-opening reaction of **4** with MeMgBr was surveyed (Table 2). The role of copper in this

Table 2. Ring Opening of Azabenzonorbornadiene **4** with Methylmagnesium Bromide Catalyzed by Various Copper Salts



4 *anti*-**9a**

entry	copper salt	conversion (%)[a]	*t* (h)	anti/syn[a]
1		0	24	
2	CuCl	85	24	90:10
3	CuI	85	24	90:10
4	$Cu(OTf)_2$	17	24	98:2
5	CuTC[b]	55	24	97:3
6	CuCN	100	2	98:2

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] CuTC = copper thiophene-2-carboxylate (ref 13).

transformation seems to be essential since no reaction took place in the absence of copper salt (entry 1). Additionally, unlike the case of oxabicyclic alkenes,[7] no other additive was needed for this reaction.[14] While most of the copper sources evaluated led to incomplete reaction after prolonged reaction time (24 h, entries 2−5), CuCN (entry 6) produced a dramatic acceleration effect in the reactivity, the reaction reaching completion in just 2 h, affording **9a** in 90% yield with virtually complete anti stereoselectivity.

The generality of the process was next investigated. Table 3 shows the results of the addition of a variety of Grignard reagents to azabenzonorbornadiene **4** in the presence of CuCN (10 mol %) in CH_2Cl_2 at room temperature. Both alkyl and aryl Grignard reagents were able to undergo ring-opening addition, providing the corresponding 1-aminodihydronaphthalenes in good to excellent chemical yields and very high

(7) Gómez Arrayás, R.; Cabrera, S.; Carretero, J. C. *Org. Lett.* **2003**, *5*, 1333−1336.

(8) For other anti-stereoselective alkylative ring-opening reactions of oxabicyclic alkenes, see: (a) Bertozzi, F.; Pineschi, M.; Macchia, F.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2002**, *4*, 2703−2705. See also: (b) Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170−7171. (c) Lautens, M.; Schmid, G. A.; Chau, A. *J. Org. Chem.* **2002**, *67*, 8043−8053.

(9) For other successful applications of (2-pyridyl)sulfonyl group in transition metal-catalyzed reactions, see: (a) Mauleón, P.; Carretero, J. C. *Org. Lett.* **2004**, *6*, 3195−3198. (b) Han, H.; Bae, I.; Yoo, E. J.; Lee, J.; Do, Y.; Chang, S. *Org. Lett.* **2004**, *6*, 4109−4112.

(10) 1,2-Dichloroethane (DCE) provided similar results, while decreased solubility of compound **4** was found in toluene. More coordinating solvents such as Et_2O, THF, or DME proved to be much less efficient.

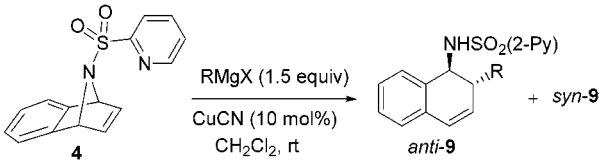
(11) CuCl was found to be the optimal copper catalyst in the case of oxabicyclic alkenes (see ref 7).

(12) Anti stereochemistry of the ring-opened products **6**−**9** was initially assigned by ^{1}H NMR, the signal of the olefinic proton at C-3 being of great diagnostic value. For compounds with syn relative configuration, such a proton appears 0.1−0.2 ppm more shielded compared to that of the anti adducts. In addition, the coupling constant of H-3 with H-2 for anti products is significantly higher (about 6.0 Hz) than that for syn compounds (roughly 3.0 Hz). The same tendency has also been observed in the coupling constants of syn and anti ring-opened products from oxabicyclic alkenes (see refs 7 and 8a).

(13) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749.

(14) Addition of Ph_3P and other commonly used ligands for copper such as BINAP or dimethyl ethylenediamine resulted in inhibition of the reaction.

Table 3. Cu-Catalyzed Ring Opening of Azabenzonorbornadiene **4** with Grignard Reagents



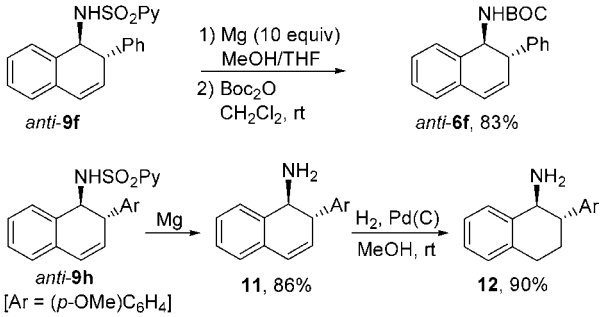
entry	X	R	product	*t* (min)	anti/syn[a]	yield[b]
1	Br	Me	**9a**	120	98:2	89
2	Br	$TMSCH_2$	**9b**	95	93:7	73
3[c]	Cl	Et	**9c**	20	>98:<2	65
4	Cl	$PhCH_2$	**9d**	20	>98:<2	53
5[c]	Cl	decyl	**9e**	20	85:15	74
6	Br	Ph	**9f**	15	>98:<2	93
7	Cl	tol	**9g**	10	>98:<2	91
8	Cl	$(p\text{-MeO})C_6H_4$	**9h**	10	>98:<2	98
9	Cl	$(p\text{-F})C_6H_4$	**9i**	20	>98:<2	92
10	Br	$3,5\text{-[bis(CF}_3)]C_6H_4$	**9j**	15	>98:<2	97
11	Br	1-naphthyl	**9k**	30	>98:<2	91
12	Br	mesityl	**9l**	480	>98:<2	87[d]
13	Br	2-thienyl	**9m**	120	>98:<2	88[e]

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Yield (%) of anti adduct after chromatography. [c] CuCl was used instead of CuCN. [d] Yield of converted product (30% of starting material was recovered). [e] Yield of converted product (25% of starting material was recovered).

anti selectivity.[12] Alkyl Grignard reagents with β-hydrogens provided better results in the presence of CuCl rather than CuCN (entries 3 and 5). Remarkably, aromatic reagents displayed very high reactivity, regardless of their electronic nature, affording ring-opened products with complete anti stereocontrol (entries 6−12). It is also interesting to note that the presence of ortho or meta substituents on the aromatic ring does not have a detrimental effect on the reactivity (entries 10 and 11), except for the very sterically hindered ortho-disubstituted mesitylmagnesium bromide, which led to incomplete reaction after 8 h (entry 12). Although less reactive, heteroaryl Grignard reagents such as 2-thienylmagnesium bromide also promoted the ring-opening reaction, affording product **9j** with good yield and complete anti stereoselectivity (entry 13).

To realize the full synthetic potential of this ring-opening protocol in stereoselective amine synthesis, the deprotection of the (2-pyridyl)sulfonamide group of products anti-**9** was readily achieved by treatment with magnesium under very mild reaction conditions (MeOH/THF, 0 °C).[15] Desulfonylation proceeded smoothly to afford cleanly the corresponding primary amine within 2 h. Thus, compound anti-**9f** was easily transformed into its Boc-derivative anti-**6f** in 83% overall yield upon deprotection with Mg and subsequent treatment of the free amine with di-*tert*-butyl carbonate at room temperature (Scheme 1). It should be noted that the diastereomeric product syn-**6f** had been previously described,[4b] which confirmed the anti relative setereochemistry of anti-**6f**.[12] In the same pursuit, compound anti-**9h** was converted into the known anti-1-amino-2-[(*p*-methoxy)phenyl]-1,2,3,4-tetrahydronaphthalene **12** (a precursor in the synthesis of an inhibitor of acyl CoA-cholesterol acyltransferase)[16] by amine deprotection and further alkene hydrogenation. This chemical correlation led us to establish unambiguously the relative anti configuration of the ring-opened products **9**.

Scheme 1. Deprotection of (2-Pyridyl)sulfonyl Group: Synthesis of 2-Substituted 1,2-Dihydro- and 1,2,3,4-Tetrahydronaphthalene-1-amines



The high reactivity, coupled with the good anti stereocontrol featured by this catalytic system, suggests that the (2-pyridyl)sulfonyl group could exert its influence on the reactivity in the ring-opening reaction via an electron-withdrawing inductive effect or/and through a coordination effect.[17] Investigation to gain insight into the mechanism of this process is currently under way.

In conclusion, the combination of a (2-pyridyl)sulfonyl moiety as an activating group at nitrogen, CuCN as a copper catalyst, and Grignard reagents as nucleophiles results in a novel and efficient anti-stereocontrolled copper-catalyzed protocol for the ring-opening reaction of azabicyclic alkenes. Each of these three elements proved to be essential for achieving good yields and excellent regio- and stereocontrol under mild reaction conditions. In addition, the process is wide in scope, tolerating both aliphatic and aromatic Grignard reagents. The enantioselective version of this method and extension of this reaction to other types of substrates, such as aziridines, is currently under investigation in our labs.

Acknowledgment. Financial support of this work by the Ministerio de Ecucación y Ciencia (Project BQU2003-0508) is gratefully acknowledged. Dr. R.G.A. thanks the Ministerio de Educación y Ciencia for a Ramón y Cajal contract. S.C. thanks the Universidad Autónoma de Madrid for a predoctoral fellowship.

Supporting Information Available: Complete description of experimental procedures and characterization data for all new compounds and copies of proton and carbon NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0478133

(15) Pak, C. S.; Lim, D. S. *Synth. Commun.* **2001**, 2209−2214.
(16) Vaccaro, W.; Amore, C.; Berger, J.; Burrier, R.; Clader, J.; Davis, H.; Domalski, M.; Fevig, T.; Salisbury, B.; Sher, R. *J. Med. Chem.* **1996**, *39*, 1704−1719.
(17) For Cu-catalyzed allylic substitution with Grignard reagents using coordinating leaving groups, see: (a) Breit, B.; Demel, P.; Studte, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3786−3789. (b) Breit, B.; Herber, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3790−3792.