ORGANIC LETTERS

2003
Vol. 5, No. 22
4235−4238

Iterative Organometallic Addition to Chiral Hydroxylated Cyclic Nitrones: Highly Stereoselective Syntheses of α,α′- and α,α-Substituted Hydroxypyrrolidines

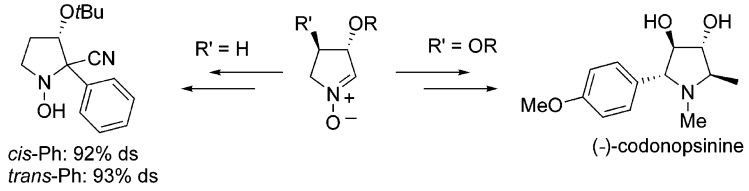
Andrea Goti,*,† Stefano Cicchi,† Vanni Mannucci,†,‡ Francesca Cardona,† Francesco Guarna,† Pedro Merino,*,‡ and Tomas Tejero‡

Dipartimento di Chimica Organica "Ugo Schiff", Università di Firenze, via della Lastruccia 13, I-50019 Sesto Fiorentino (FI), Italy, and Departamento de Química Orgánica, ICMA, Facultad de Ciencias, Universidad de Zaragoza-CSIC, E−50009 Zaragoza, Aragon, Spain

andrea.goti@unifi.it; pedro.merino@unizar.es

Received September 17, 2003

ABSTRACT



Iteration of organometallic addition to chiral hydroxylated pyrroline *N*-oxides through an addition-oxidation-addition synthetic sequence allowed highly stereoselective double alkylation of pyrrolidine at C-2 or at C-2 and C-5 depending on the regioselectivity of the oxidation step. Application of this methodology has been exemplified by the synthesis of the all-substituted pyrrolidine alkaloid (–)-codonopsinine and of proline-type amino acid precursors possessing a quaternary stereogenic center, whose configuration can be controlled.

Suitably protected chiral mono- and dihydroxypyrroline *N*-oxides of type **1** and **2** (and their enantiomers) have emerged in the past decade as extremely useful intermediates for the synthesis of chiral hydroxypyrrolidines and of more complex bicyclic azaheterocycles, such as pyrrolizidines and indolizidines.[1]

Particularly, the reactivity of **1** and **2** as 1,3-dipoles in cycloaddition reactions has been exploited toward the synthesis of pyrrolizidine and indolizidine alkaloids and several unnatural analogues.[1,2] Their reactivity as electrophiles in organometallic additions has been much less investigated.[3] A detailed and systematic study is lacking, albeit some sporadic examples of this reactivity have been reported.[4] Grignard reagents have been added to nitrones **1** for the synthesis of (−)-anisomycin,[4a] (+)-lentiginosine,[4b]

† Università di Firenze.
‡ Universidad de Zaragoza.

(1) (a) Cardona, F.; Goti, A.; Brandi, A. *Org. Lett.* **2003**, *5*, 1475−1478. (b) Cordero, F. M.; Pisaneschi, F.; Gensini, M.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **2002**, 1941−1951. (c) Socha, D.; Jurczak, M.; Frelek, J.; Klimek, A.; Rabiczko, J.; Urbańczyk-Lipkowska, Z.; Suwińska, K.; Chmielewski, M.; Cardona, F.; Goti, A.; Brandi, A. *Tetrahedron: Asymmetry* **2001**, *12*, 3163−3172. (d) Goti, A.; Cacciarini, M.; Cardona, F.; Cordero, F. M.; Brandi, A. *Org. Lett.* **2001**, *3*, 1367−1369. (e) Goti, A.; Cicchi, S.; Cacciarini, M.; Cardona, F.; Fedi, V.; Brandi, A. *Eur. J. Org. Chem.* **2000**, 3633−3645 and references therein.

(2) For recent findings on related nitrones, see: (a) Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2315−2318. (b) Toyao, A.; Tamura, O.; Takagi, H.; Ishibashi, H. *Synlett* **2003**, 35−38. (c) Duff, F. J.; Vivien, V.; Wightman, R. H. *Chem. Commun.* **2000**, 2127−2128. (d) Holzapfel, C. W.; Crous, R. *Heterocycles* **1998**, *48*, 1337−1342.

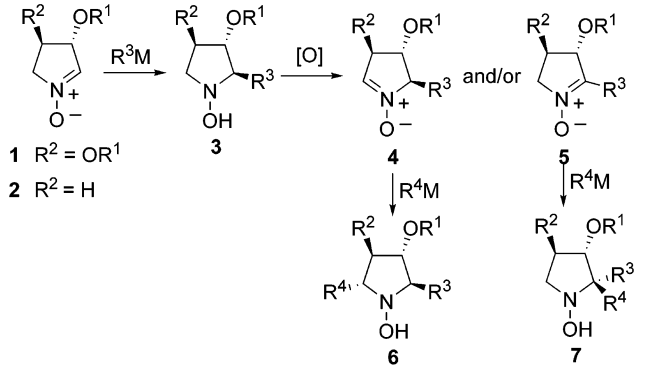
(3) For reviews of addition of organometal derivatives to nitrones, see: (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (b) Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946. (c) Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759−774. (d) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442−454. (e) Lombardo, M.; Trombini, C. *Curr. Org. Chem.* **2002**, 6, 695−713.

10.1021/ol035798g CCC: $25.00
Published on Web 10/09/2003

and biologically active tri- and tetrahydroxypyrrolidines.[4c] Murahashi has carried out a carboxymethylation of nitrone **2** with a silyl ketene acetal on the route to Geissman−Waiss lactone,[4d] and Reissig, Brandi, and co-workers have reported the addition of an allenyllithium derivative to nitrones **1** and **2**.[4e] Recently, we have reported a study on the addition of metal cyanides to nitrones **1** and **2**.[5] Apart from the first application, where the stereoselectivity of the addition was poor,[4a] in all other cases substantial high and consistent *anti* diastereoselectivity (>90%) of the addition has been observed.[4b−e,5] The stereocontrol is exerted by the vicinal protected hydroxy group, with the organometallic derivative attacking preferentially the opposite face.

The primary products of additions to nitrones are hydroxylamines, which in turn are susceptible to undergo easy oxidation to novel nitrones. Oxidation of the *N*-hydroxypyrrolidines **3** generated by a first organometallic addition to nitrone **1** or **2** followed by a further addition might open the way to pyrrolidines doubly substituted in the α-position(s) (Scheme 1).[6]

Scheme 1

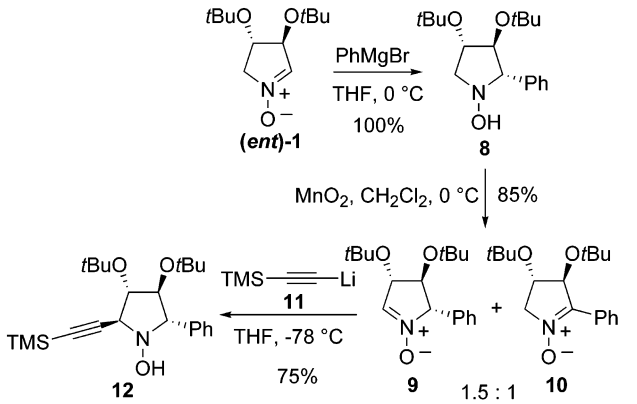


In this Letter we report the results on this iterative organometallic addition approach starting from nitrones **1** and **2** (R^1 = *t*Bu), including its applications to a novel synthesis of the all-substituted pyrrolidine alkaloid (−)-codonopsinine and to the stereocontrolled synthesis of precursors of quaternary hydroxyproline-type amino acids.

From an examination of the strategy outlined in Scheme 1, two issues arise concerning the selectivity of the overall process: (i) the diastereoselectivity connected with the two addition steps; (ii) the regioselectivity of the oxidation step. Regarding the stereoselectivity of the organometallic additions, we expected a high preference for an *anti* attack with respect to the vicinal alkoxy group, on the basis of the previous findings.[4,5] The second point is more critical and was foreseen as being strongly dependent on the starting nitrone. Indeed, on the basis of the few oxidations of 2-substituted 1-hydroxypyrrolidines to nitrones reported in the literature,[7] formation of keto nitrones **5** should be highly preferred over their regioisomeric aldo nitrones **4** by oxidation of hydroxylamines **3**. On the other hand, we have previously found that the presence of a heavily electronegative atom, as oxygen is, at C-3 has a strong influence on regioselectivity, favoring the abstraction of the vicinal anti proton.[8] This effect does not work on hydroxylamine **3** (R^2 = H) derived from nitrone **2**, which is expected therefore to give mainly a keto nitrone of type **5**. However, when nitrone **1** is used, the two effects are working in opposite directions, and hence the predominant one will control the regioselectivity of the oxidation. Therefore, formation of hydroxylamines **3** from the starting nitrones and of stereoisomers **6** and **7** from nitrones **4** and **5**, respectively, was anticipated.

These assumptions were preliminarily tested starting from the L-tartaric acid derived nitrone (*ent*)-**1**,[9] which was subjected to the planned addition-oxidation-addition sequence (Scheme 2). The first addition of PhMgBr occurred with complete diastereoselectivity to give hydroxypyrrolidine **8** quantitatively. The subsequent oxidation, as expected, furnished the two regioisomeric nitrones **9** and **10** with a scarce 60:40 selectivity in favor of the aldonitrone **9**, which after separation was reacted with lithium acetylide **11**. Also this

Scheme 2



(4) (a) Ballini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 1316−1318. (b) Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706−5707. (c) Lombardo, M.; Fabbroni, S.; Trombini, C. *J. Org. Chem.* **2001**, *66*, 1264−1268. (d) Ohtake, H.; Imada, Y.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2737−2754. (e) Pulz, R.; Cicchi, S.; Brandi, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2003**, 1153−1156.

(5) Merino, P.; Tejero, T.; Revuelta, J.; Romero, P.; Cicchi, S.; Mannucci, V.; Brandi, A.; Goti, A. *Tetrahedron: Asymmetry* **2003**, *14*, 367−379.

(6) Disubstituted pyrroline *N*-oxides have been subjected to iterative additions for the synthesis of nitroxides. See for example: (a) Keana, J. F.; Lee, T. D.; Bernard, E. M. *J. Am. Chem. Soc.* **1976**, *98*, 3052−3053. (b) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Gautier-Luneau, I.; Pierre, J.-L. *J. Org. Chem.* **1997**, *62*, 9385−9388.

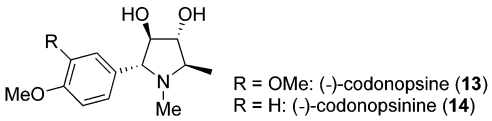
(7) (a) Cicchi, S.; Marradi, M.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **2001**, *42*, 6503−6505. (b) Cicchi, S.; Corsi, M.; Goti, A. *J. Org. Chem.* **1999**, *64*, 7243−7245. (c) Ali, Sk. A.; Hashmi, S. M. A.; Siddiqui, M. N.; Wazeer, M. I. M. *Tetrahedron* **1996**, *52*, 14917−14928. (d) Ali, Sk. A.; Wazeer, M. I. M. *Tetrahedron* **1993**, *49*, 4339−4354. (e) Murahashi, S.-I.; Sun, J.; Kurosawa, H.; Imada, Y. *Heterocycles* **2000**, *52*, 557−562. (f) Padwa, A.; Dent, W. H.; Schoffstall, A. M.; Yeske, P. E. *J. Org. Chem.* **1989**, *54*, 4430−4437.

(8) (a) Goti, A.; Cicchi, S.; Fedi, V.; Nannelli, L.; Brandi, A. *J. Org. Chem.* **1997**, *62*, 3119−3125. (b) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743−4748.

(9) Cicchi, S.; Höld, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5274−5275.

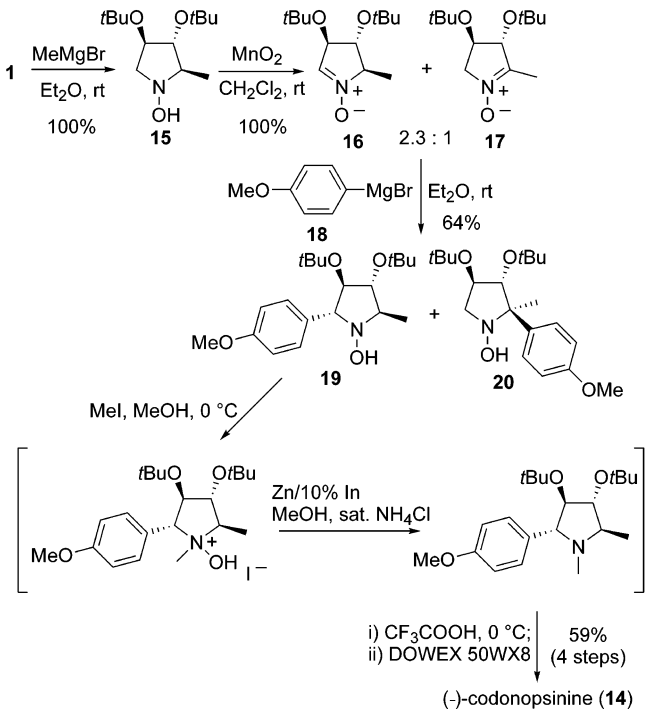
addition turned out to be completely selective, with the nucleophile entering from the opposite face with respect to the vicinal *tert*-butoxy group, thus establishing the all-*trans* stereochemistry of the resulting hydroxypyrrolidine **12**. This stereochemical pattern was unambiguously proved by X-ray structural determination of the compound obtained by desilylation of **12** followed by acetylation.

Despite the low selectivity in the oxidation of **8**, the preferential formation of aldo nitrone **9** represents a confirmation of the previously observed effect furnished by the vicinal alkoxy group,[8] which is powerful enough to override the otherwise favored formation of keto nitrone.[7] The all-*trans* stereochemical pattern of the final tetrasubstituted hydroxypyrrolidine **12** suggests that this procedure is perfectly suited to be applied to the total synthesis of several pyrrolidine alkaloids, such as (−)-codonopsine (**13**) and (−)-codonopsinine (**14**), antibiotics extracted from *Codonopsis clematidea*[10,11] exhibiting hypotensive activity without effects on CNS.[12]



Starting from D-tartaric acid derived nitrone **1** and using MeMgBr and the Grignard reagent **18** as nucleophiles in the above protocol, the hydroxypyrrolidine **19** was accessed, again with complete control of the stereochemistry (Scheme 3). Methylation of **19** followed by N-O reductive cleavage with Zn and catalytic In[13] and final deprotection of the hydroxy groups afforded the desired pyrrolidine alkaloid **14**, whose spectroscopic and analytical data were in agreement with those reported in the literature.[10−12] Several oxidants were tested for achieving the best selectivity in favor of aldo nitrone **16** from the hydroxylamine **15**. Most of them gave a quantitative yield of nitrones but with a moderate regioselectivity, with commercial MnO_2[7a] being the best performing (**16**/**17** = 70:30). For practical reasons, the mixture of nitrones was directly reacted with the Grignard reagent **18** without separation. The reaction furnished the two hydroxypyrrolidines **19** and **20**, which could be better separated at this stage. However, addition of **18** to a purified sample of nitrone **16** afforded exclusively the hydroxylamine **19**, whose stereochemistry was ascertained by NOE experiments, in 87% yield. It is noteworthy that no diastereoisomer of **20** was observed, indicating also that the attack to keto nitrone

Scheme 3



17 occurred with complete stereoselectivity, *anti* to the vicinal *tert*-butoxy group.

This finding, together with the expected high preference for oxidation to keto nitrones for hydroxylamines **3** when derived from nitrone **2**, opens the way to a selective and stereocontrolled access to 2,2-disubstituted 3-hydroxypyrrolidines **7**. This strategy was studied by using a metal cyanide as one of the nucleophiles, to synthesize precursors of hydroxyprolines and of chiral 1,2-diamines possessing a quaternary stereogenic carbon atom. When the metal cyanide was used as the first nucleophile, the process was efficient and completely selective until the formation of a keto nitrone of type **5** (R′ = CN) but then was complicated by addition of the second organometallic derivative at both nitrone and cyano functionalities. However, a reversal in the order of addition of the two nucleophiles resulted in a highly efficient overall process, which straightforwardly afforded the desired 2-cyano hydroxypyrrolidines in a stereocontrolled way (Scheme 4). Addition of PhMgBr to **2**[8b] followed by MnO_2 oxidation gave quantitatively the keto nitrone **22**. Thus, oxidation of **21** occurs with complete regioselectivity, in contrast to the analogous HgO oxidation of 2-phenyl-1-hydroxypyrrolidine, which gave a 83:17 mixture of keto to aldo nitrone.[7c] The addition of Me_3SiCN to nitrone **22** proceeded sluggishly in the absence of a Lewis acid catalyst (Table 1, entries 1 and 2). When 1 equiv of Et_2AlCl and an excess of cyanating reagent were used, the addition went almost to completion in 2 h, affording the expected cyanohydroxypyrrolidine **23** as the major diastereoisomer (Table 1, entries 3 and 4). The solvent did not affect the reaction substantially, albeit better yield and selectivity was obtained in THF than in CH_2Cl_2. However, the diastereoselectivity

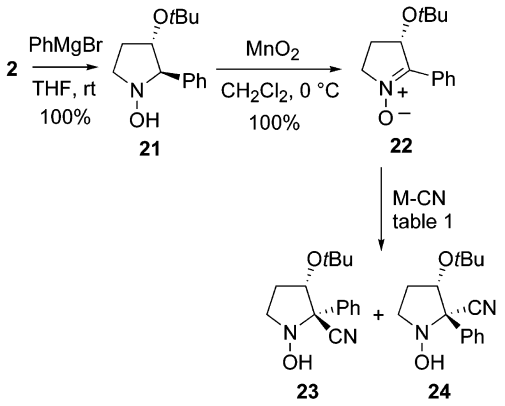
(10) Matkhalikova, S. F.; Malikov, V. M.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1969**, *5*, 30−32.

(11) A synthesis of (−)-codonopsinine by alkylation of a L-xylose-derived nitrone has been recently reported: see ref 2b. For other syntheses of **13** and **14**, see: (a) Haddad, M.; Larchevêque, M. *Synlett* **2003**, 274−276. (b) Severino, E. A.; Correia, C. R. D. *Org. Lett.* **2000**, *2*, 3039−3042. (c) Yoda, H.; Nakajima, T.; Takabe, K. *Tetrahedron Lett.* **1996**, *37*, 5531−5534. (d) Wang, C.-L. J.; Calabrese, J. C. *J. Org. Chem.* **1991**, *56*, 4341−4343. (e) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 1956−1962.

(12) Khanov, M. T.; Sultanov, M. B.; Egorova, T. A. *Farmakol. Alkaloidov Serdech. Glikoyidov.* **1971**, 210−212.

(13) Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773−1776.

Scheme 4



of the reaction was not complete, and minor amounts of product **24**, deriving from *syn*-attack of cyano to the *tert*-butoxy group, were also isolated.

Table 1. Addition of Metal Cyanides to Nitrone **22**[a]

entry	reagent (equiv)	catalyst (equiv)	solvent	conversion (%)[b]	**23**/**24** ratio
1	Me_3SiCN (3)		CH_2Cl_2	<10[c,d]	95:5
2	Me_3SiCN (3)		THF	12[c,d]	95:5
3	Me_3SiCN (3)	Et_2AlCl (1)	THF	95	92:8
4	Me_3SiCN (3)	Et_2AlCl (1)	CH_2Cl_2	91	86:14
5	Et_2AlCN (1)		THF	55	19:81
6	Et_2AlCN (1)		CH_2Cl_2	0	
7	Et_2AlCN (3)		THF	57	7:93
8	Et_2AlCN (3)		CH_2Cl_2	13	23:77
9	KCN (1.2)		CH_2Cl_2	15[e]	80:20

[a] All reactions were carried out at −20 °C for 2 h. [b] Based on integration of ^1H NMR spectra of the crude reaction mixtures. In all cases the chemical yield was quantitative (100%) with respect to the reacted nitrone. [c] The reaction was stopped after 2 weeks. [d] Further treatment with 5% methanolic citric acid of the crude mixtures afforded free hydroxylamines. [e] The reaction was carried out at room temperature for 1 h in the presence of 6 N HCl.

This result is in contrast with the complete *anti*-selectivity that we have observed in a previous study for the addition of Me_3SiCN to **1**, **2**, and other related nitrones.[5] In the same study it was found that reacting Et_2AlCN with **2** resulted in a less selective addition, still affording the *anti*-adduct as the major diastereoisomer but with a low 1.5−2:1 diastereoselection.[5] We hoped therefore that switching to Et_2AlCN in the present case, where the additional phenyl at C-2 seemed to disfavor the *anti* attack more than the *syn*, might result in a reversal of the stereoselectivity in favor of hydroxypyrrolidine **24**. Indeed with Et_2AlCN, albeit the addition was slower and gave a more modest conversion, a rewarding inversion of selectivity, up to 93:7, in favor of *cis* CN-O*t*Bu hydroxypyrrolidine **24** was found (Table 1, entries 5−8). Any attempt to complete the reaction by longer reaction time only led to extensive decomposition of the starting materials. With Et_2AlCN, the reaction showed a strong solvent dependence. When carried out in CH_2Cl_2 it went to a negligible extent only, whereas in THF with an excess of reagent it took place satisfactorily. The different mechanisms connected with the addition of Me_3SiCN or Et_2AlCN to nitrones are presumably responsible for the observed inversion of selectivity.[5] Addition of free cyanide, generated from Et_2AlCN when the reaction is quenched as observed in our previous study,[5] might also occur. With nitrone **22**, however, this possibility is negligible, since the direct addition of free cyanide, under Murahashi conditions,[4d] showed to be quite slow and **23** was obtained predominantly (Table 1, entry 9). Anyway, the possibility of accessing both diastereoisomers with remarkable selectivity simply by changing the cyanating reagent is of great synthetic significance. It is noteworthy that a quaternary carbon stereogenic center can be created in a stereocontrolled manner from a methylene unit. Compounds **23** and **24** can be considered direct precursors of chiral 2-substituted hydroxyprolines and of aminomethylpyrrolidines, which may find application in peptidomimetics and catalysis, respectively.

In conclusion, the synthetic sequence involving nucleophilic addition-oxidation-nucleophilic addition to tartaric and malic acids derived nitrones **1** and **2** has been studied employing two different organometal derivatives. The process allows high levels of diastereocontrol, as demonstrated in the application to the syntheses of the fully substituted pyrrolidine alkaloid (−)-codonopsinine and of 2,2-disubstituted 3-hydroxypyrrolidines. Studies are currently underway in our laboratories in order to extend the range of substrates and nucleophiles used and to devise other useful applications in organic synthesis.

Acknowledgment. We thank MIUR, Italy (Cofin 2002), MCYT, Spain, FEDER Program (Project CASANDRA, BQU2001-2428), and the Government of Aragon (Project P116-2001), Spain for financial support, MIUR and MCYT for a bilateral exchange project (2000-2001). V.M. was a Socrates/Erasmus (Firenze-Zaragoza) fellow.

Supporting Information Available: Experimental procedures and analytical and spectroscopical characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035798G