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Enantioselective approach to butenolides upon reduction of alkoxycarbene complexes of chromium with chiral dihydropyridines

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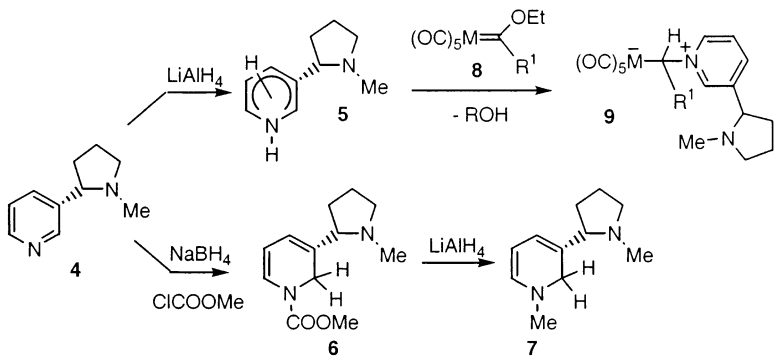
Abstract—Chromium alkoxycarbene complexes tethered to a triple bond react with a series of chiral dihydropyridines, among which is *N*-methyl-1,2-dihydronicotine, to give enantioselectively, upon cascade insertion reactions, polycyclic butenolides.

The enantioselective formation of organic compounds via non-chiral carbene fragments from Fischer carbene complexes has only met, up to now, with very limited transformations: indeed, only an early example in which the metal bore, besides the carbene, a chiral phosphine, described the synthesis of optically active cyclopropanes upon its interaction with an olefin.[1,2]

Very recently, we discovered a new application of Fischer carbene complexes for the synthesis of a broad spectrum of butenolides **3** via the intramolecular incorporation of a triple bond and two CO ligands, induced by the metal, and triggered by dihydropyridines (Scheme 1).[3–6] The key steps in these transformations are a hydride transfer from *N*-methyldihydropyridines to the carbene carbon of the various complexes **1** leading first to metal pyridinium alkylates **2**, and a final protonation at the ring junction, each operation leading to a new stereocenter.

We felt that such a transformation was ideally suited for attempts to an enantiomeric approach to butenolides, on the one hand by the use of chiral reducing agents, which would parallel the biomimetic reduction of carbonyl compounds with NADPH and its models,[11–13] on the second hand, by carrying out enantioselective protonations.

The reasons behind our expectations were the following: first, a wealth of chiral dihydropyridines are known to reduce enantioselectively carbonyl compounds. Second, the dihydronicotines **5** and **7**, easily obtained from (*S*)-(−)-nicotine **4** reacted like simple dihydropyridines with alkoxycarbene complexes **8** to give, in the case of



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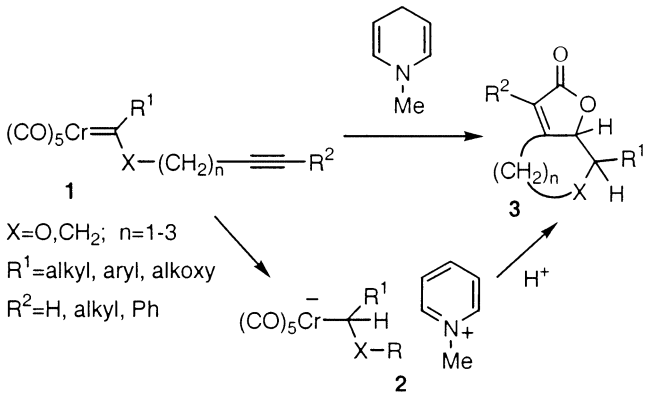
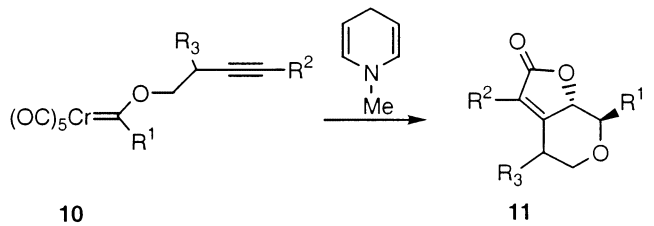
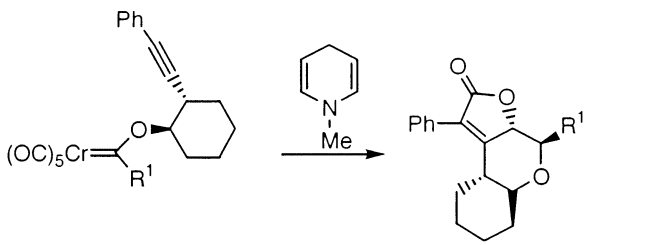


Scheme 1.

5, upon transfer of a hydride, the expected, stable dihydronicotinium ylid complexes **9**.[3]

The purpose of this communication is thus to report on the enantiodifferentiating reductions of a series of carbene complexes leading to optically active butenolides.

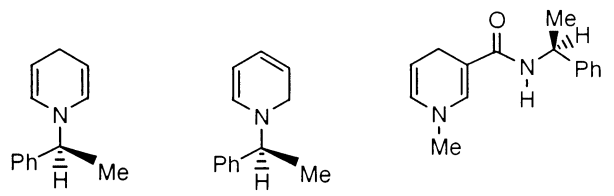




12a R^1=Ph **13a** 74%
12b R^1=Cyclopropyl **13b** 53%

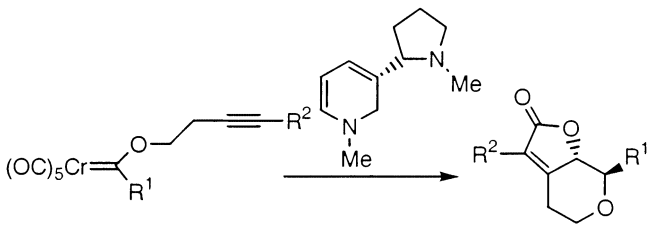
High diastereoselectivity for the reduction of carbene complexes **10** with *N*-methyl dihydropyridines had already been established.[3] This was impressively confirmed in the case of complexes **12a** and **12b** which led *diastereospecifically* to **13a** and **13b** in 74 and 53% yield, respectively. Compound **13a** was fully characterized by an X-ray structure analysis.[7]

These and previous results, urged us to carry out the same transformations with the aforementioned chiral dihydropyridines **7**, but also with the dihydropyridines **14**, **15** and **16** prepared according to the literature.[8,9]



Typically, when a dichloromethane solution of complex **10a** was subjected to (*S*)-(1-phenylethyl)-1,4-dihydropyridine **14** at –40°C, then slowly heated to room temperature over 12 h, the butenolide **11a** was indeed obtained as a single isomer, in 62% yield but, according to chiral GC, as a racemic mixture. Moving to the isomeric 1,2-dihydropyridine **15** an encouraging enantioselection (ee, 27%) was observed. Similarly, the use of the chiral dihydronicotinamide **16**, a close analog of the natural dihydropyridines, led indeed to the expected butenolide in 55% yield, but again with a disappointing 4% ee. Since the best result was observed for a dihydropyridine in which the chiral center is β with respect to the transferable hydride, we attempted the reaction with the chiral *N*-methyl-1,2-dihydronicotine **7**: under similar conditions as for *N*-methyldihydropyridine, the butenolide **11a** could be isolated as a single isomer with, according to chiral GC, an enantiomeric excess of 33%. This excess increased to 55% when **10c** was used instead. As can be seen, the same behavior was observed for all the complexes examined so far.

It appears first that whereas the nature of the substituent on the triple bond is of no influence on the enantiomeric excess, the nature of the substituent on the carbene carbon is fundamental. Second, according to these preliminary results (not optimized), the yields of butenolides are lower in most of the cases, but for **10a**, when compared to the yields observed for the same reactions with *N*-methyldihydropyridine.[2,7,10]



10a	R^1=Ph, R^2=H	**11a** 63%	ee=33%
10b	R^1=Ph, R^2=Ph	**11b** 38%	ee=30%
10c	R^1=Me, R^2=H	**11c** 25%	ee=55%
10d	R^1=Cyclopropyl, R^2=H	**11d** 32%	ee=15%
10e	R^1=Cyclopropyl, R^2=Ph	**11e** 40%	ee=11%

A common feature for all the transformations depicted herein is the creation of two new contiguous stereocenters upon addition of a hydride and a proton as the initiator and the terminator of the cascade insertions. This leads, in the general case, stereospecifically to the more stable products in which the heterocyclic ring substituents are *trans* and in equatorial positions. In the case of the chiral dihydropyridines, one can assume that the enantiomeric differentiation is the result of the formation of two diastereomeric intermediates upon interaction of the carbene complexes and the dihydropyridines prior to the hydride transfer. Such intermediates would thus mimic the ternary complexes ketone:dihydropyridine:Mg^{2+} which have been put to the fore in the case of the enantiomeric reductions of ketones by NADPH and its models.[11–13] An important point seems to arise from these preliminary results, the

distance between the hydride to be transferred and the chiral center since 1,2-dihydroprydines are more efficient in terms of enantioselectivity than 1,4-dihydropyridines. Such an observation had already been made for the enantioselective reduction of carbonyl compounds with NADH mimics, and confirms again the parallel which exits between carbonyl compounds and carbene complexes.

Modification of the structure of the reducing agents (e.g. of dihydronicotine) or the use of related more elaborate dihydropyridines along with attempts at carrying out enantioselective protonations are in progress and might be ways to improve the encouraging enantioselectivities already observed in these cascade insertions.

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References

1. Cooke, M. D.; Fischer, E. O. *J. Organomet. Chem.* **1973**, *56*, 279.
2. For references on reactions involving either chiral complexes or chiral substrates, see: (a) Wulff, W. D. *Organometallics* **1998**, *17*, 3116; see also: (b) Hegedus, L. S. *J. Am. Chem. Soc.* **1982**, *104*, 5538; Lugan, N.; Kelley, C.; Terry, M. R.; Geoffroy, G. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1990**, *112*, 3220; (c) Brookhart, M.; Timmers, D.; Tucker, J. R.; Williams, G. D.; Husk, G. R.; Brunner, H.; Hammer, B. *J. Am. Chem. Soc.* **1983**, *105*, 6721; (d) Soderberg, B. C.; Hegedus, L. S.; Sierra, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 4364; (e) Bouancheau, C.; Parlier, A.; Rudler, M.; Rudler, H.; Vaissermann, J.; Daran, J. C. *Organometallics* **1994**, *13*, 4708; (f) For carbene complexes derived from sugars, see for example: Weyershausen, B.; Dötz, K. H. *Eur. J. Inorg. Chem.* **1999**, 1057; (g) Jäkel, C.; Dötz, K. H. *Tetrahedron* **2000**, *56*, 2167; (h) For relative asymmetric syntheses of polycyclic systems, see: Yan, J.; Zhu, J.; Matasi, J. J.; Herndon, J. W. *J. Org. Chem* **1999**, *64*, 1291.
3. Rudler, H.; Parlier, A.; Certal, V.; Vaissermann, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3417.
4. Rudler, H.; Parlier, A.; Durand-Réville, T.; Martin-Vaca, B.; Audouin, M.; Garrier, E.; Certal, V.; Vaissermann, J. *Tetrahedron* **2000**, *56*, 5001.
5. Rudler, H.; Parlier, A.; Martin-Vaca, B.; Garrier, E.; Vaissermann, J. *J. Chem. Comm.* **1999**, 1439.
6. For other examples of multiple CO and alkyne insertion reactions, see: (a) Semmelhack, M. F.; Tamura, R.; Schnatter, W.; Springer, J. *J. Am. Chem. Soc.* **1984**, *106*, 6363; (b) Yao-Chang, X.; Challener, C. A.; Dragisich, V.; Brandvold, T. A.; Peterson, G. A.; Wulff, W. D. *J. Am. Chem. Soc.* **1989**, *111*, 7269; (c) Bao, J.; Wulff, W. D.; Dragisich, V.; Wenglowsky, S.; Ball, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 7616.
7. Crystal data for **13a**: $C_{23}H_{22}O_3$, space group $P2_12_12_1$, $Z=4$, Mo Kα radiation ($\lambda=0.71069$ Å), $a=9.145(2)$, $b=10.484(4)$, $c=19.256(6)$ Å, $V=1846(1)$ Å^3, refinement on F^2, $R(F)=5.36\%$, $wR(F^2)=5.80\%$, GOF = 1.13 for 236 parameters and 1514 unique reflections with $(F_o)^2 > 1.5\sigma(F_o)^2$.
8. (a) Wong, Y.-S.; Marazano, C.; Gnecco, D.; Das, B. C. *Tetrahedron Lett.* **1994**, *35*, 707; (b) Mehmandoust, M.; Marazano, C.; Singh, R.; Gillet, B.; Cesario, M.; Fourrey, J.-L.; Das, B. C. *Tetrahedron Lett.* **1988**, *29*, 4423; (c) Genisson, Y.; Marazano, C.; Mehmandoust, M.; Gnecco, D.; Das, B. C. *Synlett* **1992**, 431.
9. Combret, Y.; Torché, J.-J.; Plé, N.; Duflos, J.; Dupas, G.; Bourguignon, J.; Quéguiner, G. *Tetrahedron* **1991**, *47*, 9369.
10. The low yield for complexes in which $R^1 = Me$ is mainly due to their decomposition by α-elimination.
11. Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1.
12. Leroy, C.; Levacher, V.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Tetrahedron: Asymmetry* **1997**, *19*, 1109.
13. Ohno, A.; Oda, S.; Ishikawa, Y.; Yamazaki, N. *J. Org. Chem.* **2000**, *65*, 6381.