ORGANIC LETTERS

2011
Vol. 13, No. 9
2294–2297

Cyclohydrocarbonylation-Based Strategy toward Poly- Substituted Piperidines‡

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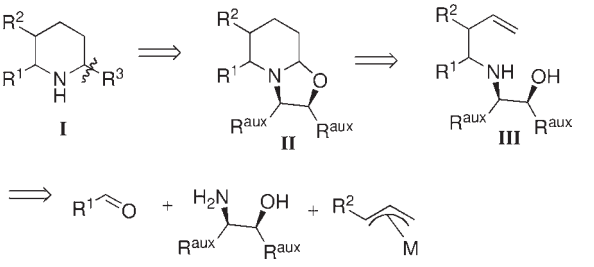
Received March 1, 2011

ABSTRACT

Convenient accesses to enantiomerically pure 2-, 2,3-, 2,6-, 2,3,6-substituted piperidines and 1,4-substituted indolizine are described. At first, indium-mediated aminoallylation and -crotylation of aldehydes with (*R*)-phenylglycinol or (1*R*,2*S*)-1-amino-2-indanol gave homoallylamines with high stereocontrol. Then, these products, submitted to a Rh(I)-catalyzed hydroformylative cyclohydrocarbonylation, afforded perhydrooxazolo [3,2-*a*]piridines whose oxazolidines are opened with nucleophiles. Finally, the removal of the chiral auxiliaries delivered the enantiomerically pure piperidines.

Cyclohydrocarbonylation (CHC) is a powerful method to prepare heterocycles.[1] Recently, we demonstrated that CHC can be applied to domino[2] or multicomponent[3] syntheses of oxazolopyridinones via acyliminium intermediates. Extension of the procedure to enantiomerically pure homoallyl amines could allow a direct access to substituted piperidines.[4,5] Therefore we envisaged a strategy with the following steps (Scheme 1): (i) assembly of different homoallyl amines via allyl organometallic reagents and aldehydes in the presence of amino-alcohols as chiral auxiliaries; (ii) stereocontrolled CHC of the resulting amines to generate oxazolopiperidines; (iii) ring-opening of the oxazolidines via organometallic based nucleophiles to install substituents on the heterocyclic ring; (iv) final removal of the chiral auxiliaries.

Scheme 1



† Dedicated to Professor Alfredo Ricci on the occasion of his retirement for his authoritative contribution to organometallic chemistry and catalysis.

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10.1021/ol200557r
Published on Web 04/04/2011

The choice of the residues on the aldehyde, the structure of allyl reagents, and the nucleophiles would build piperidines with substituents at C-2, C-3, and C-6. As these heterocycles are present in several natural products and have important roles in medicinal chemistry, simple general synthetic approaches are desirable.[5] In this paper, we propose a new strategy, in line with this objective, based on CHC reactions.

To prepare intermediates **III** (Scheme 1), the Barbier-type allylation of *N*-alkylimines with allyl bromide and indium in alcoholic medium[6] was explored. (*R*)-Phenylglycinol has been reported in this reaction as a useful chiral auxiliary for the construction of optically active amines.[7]

Aldehydes **1**−**8** reacted with allylbromide **12** in the presence of indium (**9**) and (*R*)-phenylglycinol (**10**) or (1*R*,2*S*)-1-amino-2-indanol (**11**) in MeOH giving homoallyl alcohols **15**−**22** in good yields and stereoselectivity (Table 1, entries 1−8). This result encouraged us to explore the reaction with more synthetically useful bromides **13** or **14**.[8] In this case, the formation of only two of the four possible diastereomers was observed. However, with (*R*)-phenylglycinol (**10**) and aliphatic aldehydes, a good stereoselectivity was obtained wheras a 1:1 mixture was observed with benzaldehyde (entry 10, compound **24**). Using the more hindered auxiliary **11** the expected product were always formed with high stereoselectivity (entries 11−14 (**25**−**28**) in Table 1).[9]

Compounds **15**−**23** and **25**−**28**, each bearing a terminal alkene, were then submitted to hydroformylation using syngas (H_2/CO 1/1) in the presence of Rh(I). As the linear aldehyde was desired in our initial specifications, a selection of the appropriate ligand for Rh(I) has to be made. The domino hydroformylation cyclization on alkenes with amino alcohol appendages has never been explored before, as we[2,3] and others[1d−f] have mostly described the reaction on the corresponding amides passing through a reactive acyliminium ion. Indeed, the present substrates **15**−**28**, encompassing heteroatoms (O or N), could possibly compete as ligand for the metal during the hydroformylation.

After some experimentations, we were pleased to discover that CHC occurred using $Rh(CO)_2$acac in the presence of biphephos (5 mol % of Rh catalyst, 1:5 ratio with the phosphite) under H_2/CO (8 bar) in THF at 70 °C (4−12 h).[9] This result is accounting for the capability of biphephos to coordinately embrace Rh(I). Variations of the reaction temperature or use of microwave dielectric heating, in order to shorten the reaction time, did not produce an improvement at all. The diastereoselectivity in the CHC reaction was dependent from the nature of the chiral auxiliary. With (*R*)-phenylglycinol, acceptable dr were obtained exclusively when an aromatic fragment was present at C-2 (compare entry 1 with entries 2−4 in Table 1) Better results were again achieved when the (1*R*,2*S*)-1-amino-2-indanol moiety was attached to the substrates. On products **23**−**28**, derived from crotyl bromides **13** or **14**, CHC occurred with the same trend previously observed on **15**−**22**. In the case of CHC products derived from crotyl bromides **13** and **14**, the relative stereochemistry was established through the X-ray analysis of crystalline **39** (Figure 1).

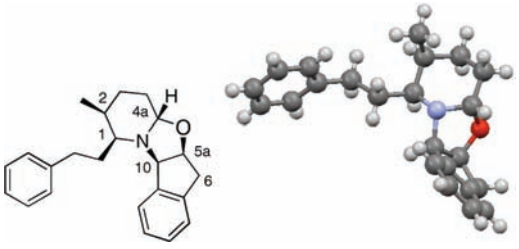
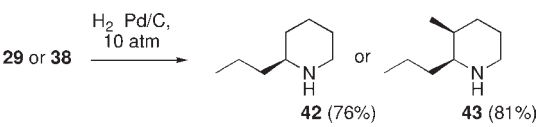


Figure 1. X-ray structure of compound **39**.

A *cis* relation between the hydrogens at C-1, C-2, and C-10 was revealed, whereas at the ring junction, the hydrogen at C-4a has a *trans* relationship in respect to the ones at C-1 and C-2. In compound **39**, NOE interactions were found between H1−H2 and H1−H10, and similar interactions could be found with compounds **38**, **40**, and **41** confirming that their respective stereochemistries are similar to the one found in **39**.

Perhydro-oxazolopyridines obtained with this process can be elaborated in different ways. Using hydrogenolysis of the auxiliary in substrates **29** or **38**, (*S*)-(+)-coniine **42**, and 2,3-disubstituted piperidine **43** were obtained in good yields (Scheme 2).

Scheme 2



Alternatively, the oxazolidine ring can be opened with a nucleophile in order to introduce an additional substituent at C-6. When oxazolidines **35** or **36** were submitted to

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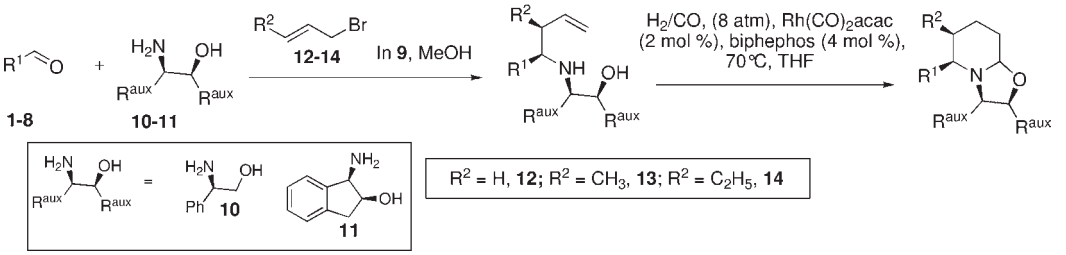
(9) Allylation chemistry was carried out at rt (20 °C), as lower temperatures decreased yields without improvements in stereoselectivity.

Table 1. Cyclohydrocarbonylation-Mediated Synthesis of Perhydrooxazolo[3,2-*a*]pyridines



entry	aldehyde	amino alcohol/ bromide	homoallyl amine (yield;[a] dr[b])	CHC product (yield;[a] dr[b])	entry	aldehyde	amino alcohol/ bromide	homoallyl amine (yield;[a] dr[b])	CHC product (yield;[a] dr[b])
1	$R^1 = C_3H_7$- **1**	**10 / 12**	**15** (86%; >99:1)	**29** (78%; 55:45)	8	R^1= 2-furyl **8**	**11/ 12**	**22** (78%; 92:8)	**36** (75%; 97:2)
2	R^1= $Ph(CH_2)_2$- **2**	**10/ 12**	**16** (70%; 97:3)	**30** (73%; 98:2)	9	**1**	**10/ 13**	**23** (60%; 90:10)	**37** (67%; 60:40)
3	$R^1 = PhCH_2$- **3**	**10/ 12**	**17** (85%; >99:1)	**31** (95%; 83:17)	10	**5**	**10/ 13**	**24** (76%; 56:44)	--
4	$R^1 = BnOCH_2$ **4**	**10/ 12**	**18** (60%; 98:2)	**32** (63%; 70:30)	11	**1**	**11/ 13**	**25** (70%; 95:5)	**38** (73%; 97:3)
5	R^1 = Ph **5**	**11/ 12**	**19** (65%; 91:9)	**33** (63%; 85:15)	12	**2**	**11/ 13**	**26** (97%; 98:2)	**39** (73%; 99:1)
6	R^1= $Ph(CH_2)_2$- **2**	**11/ 12**	**20** (83%; >99:1)	**34** (72%; 98:2)	13	**7**	**11/ 13**	**27** (64%; 94:6)	**40** (69%; 85:15)
7	$R^1 = C_{12}H_{25}$- **7**	**11/ 12**	**21** (61%; 98:2)	**35** (75%; 96:4)	14	**2**	**11/ 14**	**28** (68%; 94:6)	**41** (78%; 85:15)

[a] Isolated yields. [b] Diastereomer ratio determined by ^{1}H NMR of the crude reaction mixtures.

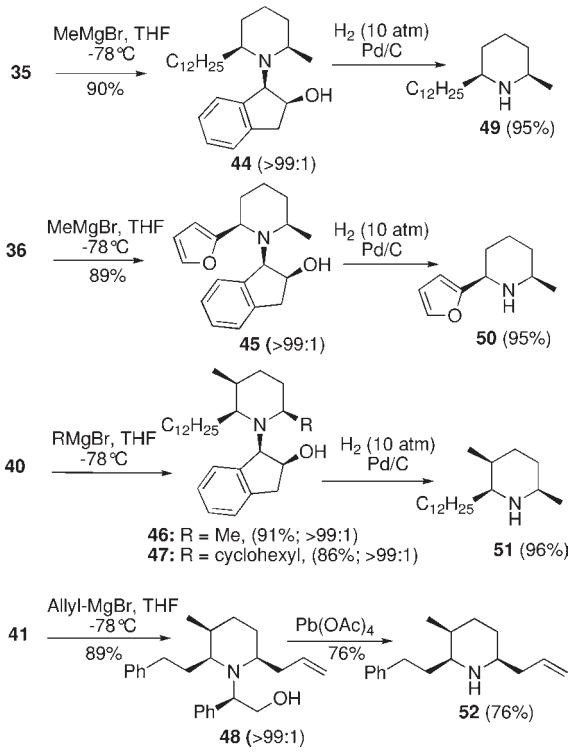
reaction with MeMgBr, exclusively the *cis* compounds **44** or **45** were obtained in good yields (NOE experiments). In addition, the mixture of diasteromeric oxazolidines **40** (85:15) reacted with MeMgBr or cyclohexyl-MgBr yielding compounds **46** and **47** as single diastereomers, as shown by ^{1}H and ^{13}C NMR analysis (Scheme 3).

A similar behavior has been previously observed with other oxazolidines and Grignard reagents.[10] Closing hydrogenolysis gave 2,6-disubstituted and 2,3,6-trisubstituted piperidines **49**–**51**. When an allyl group was present on the piperidine scaffold (**48**), removal of the chiral auxiliary with $Pb(OAc)_4$ allowed the survival of the C–C double bond (**52** in Scheme 3).[11] A practical

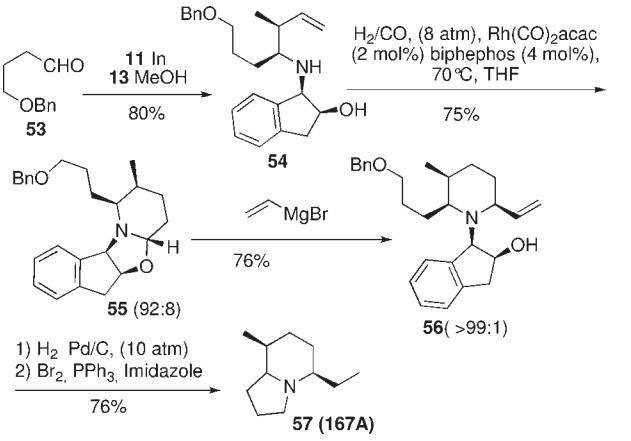
(10) The observation that either diastereomer led to the same stereoisomer suggests the formation of an intermediate hydroxy iminium ion. See: (a) Poupon, E.; François, D.; Kunesch, N.; Husson, H.-P. *J. Org. Chem.* **2004**, *69*, 3836–3841. (b) Katritzky, A. R.; Qiu, G.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1998**, *63*, 6699–6703.

(11) $Pb(OAc)_4$ was reported to remove (−)-4-isopropyl-2-aminoindanol from 2,4,6-trisubstituted piperidines prepared using this chiral auxiliary: Kobayashi, T.; Hasegawa, F.; Tanaka, K.; Katsumura, S. *Org. Lett.* **2006**, *8*, 3813–3816.

Scheme 3



Scheme 4



application of this protocol toward the synthesis of the indolizine alkaloid 167A (**57**)[12] is reported in Scheme 4. Starting from aldehyde **53**, the standard protocol relaying on enantioselective allylation and CHC was performed. Then the C2 chain was inserted using vinyl-MgBr to deliver adduct **56**. Final hydrogenolysis removed the chiral auxiliary and the protective group and produced the saturated C2 chain. The synthesis was completed using a reported procedure[13] giving **57** (34% overall yields in only five steps).

In conclusion, we explored the stereochemistry of the In-mediated allylation and crotylation of different aldehydes, highlighting limits and potential of the method, and prepared a series of 2-, 2,3-, 2,6-, or 2,3,6-susbtituted enantiomerically pure piperidines and one indolizidine using a combination of amino-allylation of aldehydes assisted by In and a subsequent CHC reaction, an approach potentially suitable for the preparation of many other azaheterocycles. Efforts in this direction are in progress in our group.

Acknowledgment. Partial financial support from Sienabiotech spa (Siena) is gratefully acknowledged.

Supporting Information Available. Detailed experimental procedures and spectral and analytical data for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) This is the first total synthesis of this alkaloid. An attempted structure determination has been previously described: Daly, J. W.; Myers, C. W.; Whittaker, N. *Toxicon* **1987**, *25*, 1023–1030.

(13) Stoye, A.; Quandt, G.; Brunnhöfer, B.; Kapatsina, E.; Baron, J.; Fisher, A.; Weymann, M.; Kunz, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2208–2230.