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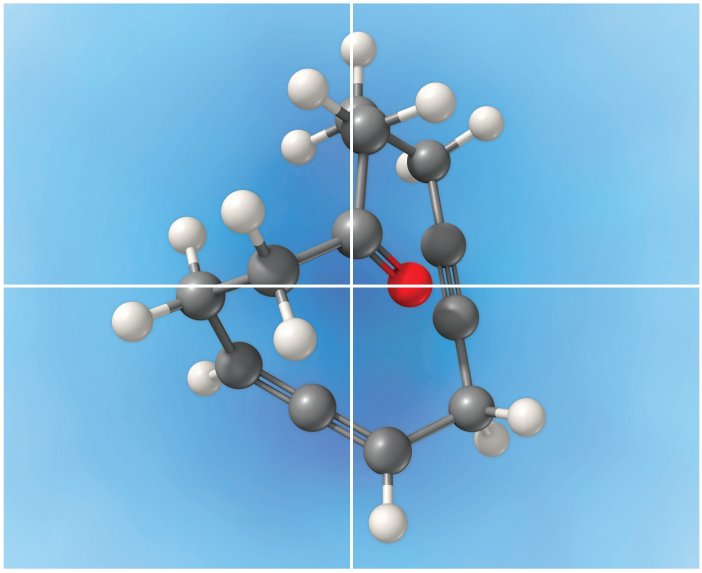

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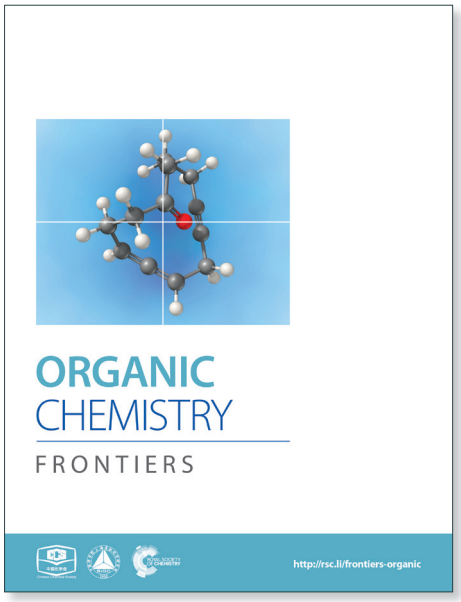


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# A Highly Stereocontrolled Protocol to Prepare Pipecolic Acids Based on Heck and Cyclohydrocarbonylation Reactions

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A novel synthetic protocol based on In mediated glyoxylate allylation, Heck coupling and Rh catalysed cyclohydrocarbonylation (CHC) was established in order to access enantiomerically pure polysubstituted pipecolic acids. The key steps are the Heck reaction, performed exclusively using a phenone-oxime derived palladacycle and the domino hydroformylation-cyclisation of the styryl derivative obtained from the Heck coupling. The reaction scheme, proceeding with good stereoselectivity, is also suitable to prepare substituted piperidine derivatives.

## Introduction

L-Pipecolic acid is a non-coded amino acid present in a variety of natural products as secondary metabolites derived from bacteria, fungi and plants.[1] It is a key element in pharmacologically relevant molecules as antibiotics,[2] anesthetics,[3] immunosuppressive and anticancer drugs[4] (Figure 1). Pipecolic acid derivatives behave also as proline analogues, inducing β-turns in peptidomimetics[5] and recently it received great attention as ligand for organocatalytic processes.[6]

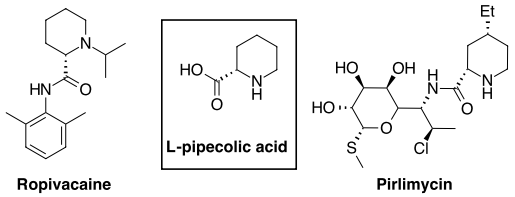
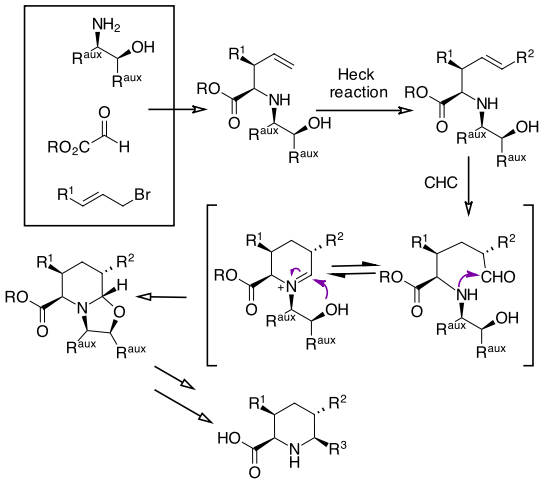



**Figure 1**

This synthetic and biological versatility stimulated the development of several approaches for pipecolic acid preparation including biocatalysis,[7] photocatalysis,[8] ring closing metathesis,[9] chiral aziridine rearrangments[10] and many others, recently reviewed.[11] Domino hydroformylation-cyclisation of olefins containing a nitrogen nucleophile (cyclohydrocarbonylation, CHC)[12] is a powerful method to prepare multifunctional heterocycles such as, for example, indolizidine,[13] tetrahydroquinolines,[14] quinolizidines[15] and piperidines.[16, 17]

We thought to expand the scope of our CHC process for piperidine synthesis[17] with the aim of preparing enantiomerically pure di- and tri-substituted pipecolic acids (Scheme 1).

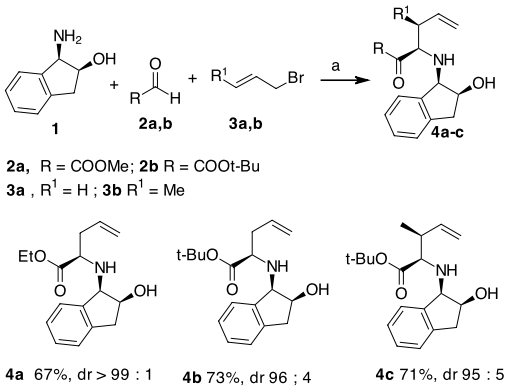



**Scheme 1** Planned synthesis of polysubstituted pipecolic acids.

Appling the amino alcohol/Indium mediated multicomponent allylation reaction to glyoxylic acid derivatives we planned to obtain a 4-pentanoic acid derivative that could be further functionalized by an Heck reaction. Then, a Rh catalyzed CHC followed by oxazolidine ring opening and chiral auxiliary removal, should give 5,6- or 3,5,6-trisubstitued pipecolic acids.

## Results and discussion

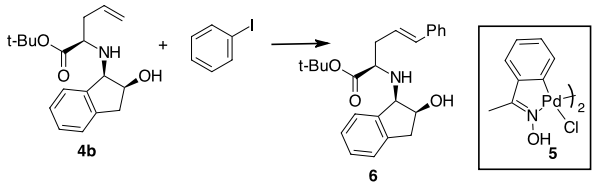
Initially, the allylation reaction with glyoxylic acid derivatives was investigated. Based on our previous result, (1*R*,2*S*)-1-amino-2-indanol **1** was selected as the chiral auxilary.[17] The imines generated in situ starting from **1** and aldehydes[18] **2a, 2b** were exposed to indium powder in the presence of allyl or crotyl bromide in alcoholic medium.[19] In all the cases, the desired products **4a-c** were obtained in good yields and excellent diastereoselectivity (Scheme 2) confirming that indanol is a good choice as auxiliary for enantioselective Barbier type allylations. The product sterochemistry was established on the analysis of the further cyclisation compounds (see below).




**Scheme 2**. a. In (3 eq.), 3 (2 eq.), EtOH, r.t., 3h

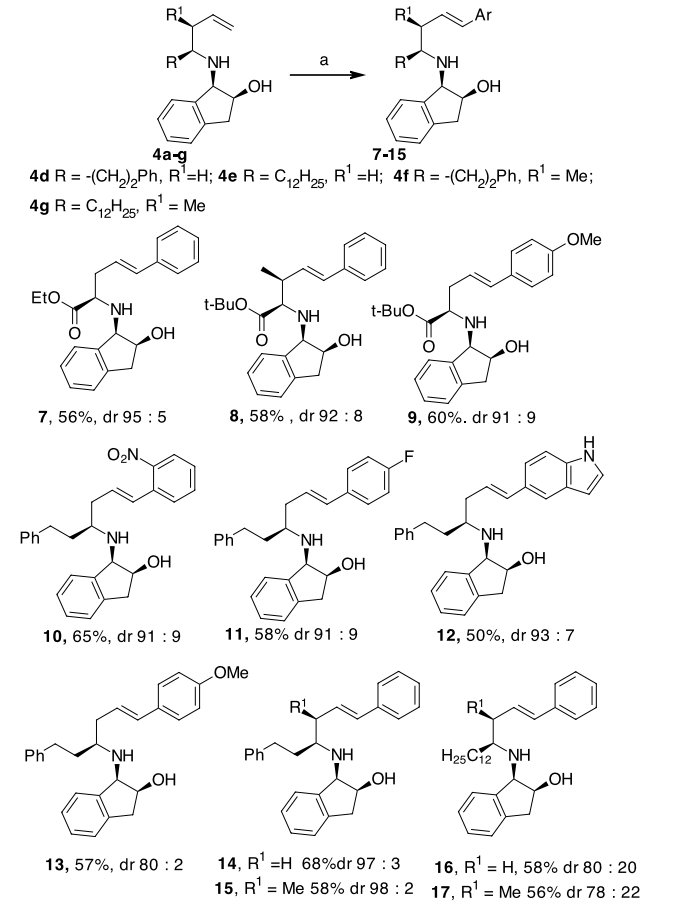
A possible functionalization of the allyl derivatives **4a-c** was investigated *via* an Heck Pd-catalysed reaction (Table 1). This protocol in suitable for the synthesis of 5-aryl pipecolic acids and also for 5-aryl piperidine derivatives, a series of products scarcely investigated to date.[20]

Table 1 Exploration of Heck reaction




| Entry | Catalyst[a] | Additives/solvent | Conditions | Yield% |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $Et_3N$ (2 eq.), toluene | reflux, 12 h | - |
| 2 | $Pd(OAc)_2$ | $Et_3N$ (2 eq.), $PPh_3$ (4 mol%) toluene | reflux, 12 h | - |
| 3 | $Pd(OAc)_2$ | $Et_3N$ (2 eq.), $PPh_3$ (4 mol%), DMF | 90 °C, 12 h | - |
| 4 | $Pd(OAc)_2$ | $Et_3N$ (2 eq.), DMF | 20 °C, 20 min | - |
| 5 | $Pd(OAc)_2$ | $Et_3N$ (2 eq.), $PPh_3$ (6 mol%), DMF | MW, 120 °C, 60 min | - |
| 6 | $Pd(PPh_3)_4$ | $Et_3N$ (2 eq.), DMF | 120 °C, 12 h | 15% |
| 7 | $Pd(PPh_3)_4$ | DIPEA (2 eq.), DMF | 120 °C, 12 h | 19% |
| 8 | $Pd(PPh_3)_4$ | $K_2CO_3$ (3 eq.), DMF | 120 °C, 12 h | 12% |
| 9 | $Pd(PPh_3)_4$ | $K_3PO_4$ (4 eq.), DMF | 120 °C, 12 h | 12% |
| 10 | **5** | $Et_3N$ (1.3 eq.), DMF | 120 °C, 12 h | 46% |
| 11 | **5** | $Et_3N$ (1.3 eq.), DMF | 120 °C, 20 min | 55% |

Compound **4b** was selected for tuning the conditions of the Heck coupling. When **4b** and iodobenzene were submitted to classical Heck reaction conditions using $Pd(OAc)_2$, $Et_3N$, and $PPh_3$ in refluxing toluene for 12 h, no reaction occurred (Table 1, entry 1-2). Even using DMF as the solvent at 90 °C or 120 °C, under traditional or microwave (MW) dielectric heating, only the starting materials were recovered (Table 1, entry 3 and 5). A partial conversion into **6** was observed using $Pd(PPh_3)_4$, $Et_3N$ in DMF at 120 °C for 12 h (Table 1, entry 6). However, no improvements were obtained changing the base from $Et_3N$ to DIPEA, $K_2CO_3$ or $K_3PO_4$ (Table 1, entries 7-9). After exploring different Pd sources and ligands, the best reaction conditions were finally identified using Pd catalyst **5**, without phosphorous ligands, in the presence of $Et_3N$ in DMF as the solvent. This palladacycle can be easily prepared from accessible *p*-methoxy acetophenone oxime and $Li_2PdCl4$.[21] It gave excellent results especially when used immediately after isolation. Reaction of **4b** with iodobenzene gave the desired internal alkene **6** in good yield and stereoselectivity toward the E-isomer.[22] Moreover, while $Pd(PPh_3)_4$ gave effective conversion in 4% mol amounts, catalyst **5** gave product **6** when used in 1% mol amount respect to starting **4b**.



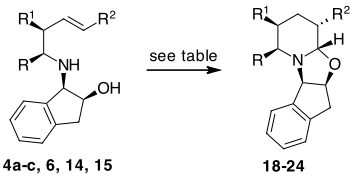

**Scheme 3** a: **5** (0.01 mol%), $Et_3N$ (1.3 eq.), ArI (1 eq.), DMF, MW, 120 °C, 20 min.

Comparable results were obtained under traditional heating (120 °C, 12 h, Table 1, entry 10) or under MW dielectric

heating (120 °C, 20 min Table 1, entry 11).The best conditions found were successfully applied to **4a** and **4c** and also to other homoallylic derivatives **4d-g** prepared as previously reported (Scheme 3). In all the examples investigated, the use of palladacyle **5** allowed the isolation of the coupling products in good yield, even working with substituted- and hetero-aryl iodides (Scheme 3). All the products were formed with excellent diastereoselectivities except in the case of compounds **16** and **17**, where a long aliphatic chain was present in the homo-allyl position. The substituent present on the allyl position, seemed to have a minor impact in the E/Z ration of the Heck product respect to the substituent farther from the reaction centre (compare yields and dr of products **15** and **17** in Scheme 3). Compounds **8**, **15** and **17** were isolated as single diasteroisomers, suggesting that Pd mediated isomerisation of the double bond did not occur.

A selection of the terminal and internal alkenes synthesized (compounds **4a-c**, **14** and **16**) was then subjected to CHC conditions: 7 bar of $CO/H_2$ in the presence of $[Rh(acac)(CO)_2]$ and BIPHEPHOS (6,6′-[(3,3′-di-tert-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diyl)bis(oxy)]bis(dibenzo[d,f][1,3,2]dioxa-phosphepin), in THF for 12 h at 70 °C (Table 2).

Table 2 Cyclohydrocarbonylation reaction




**4a-c, 6, 14, 15** **18-24**

| Entry | sm | Conditions[a] | R, $R^1$, $R^2$ product, yield%, dr |
|---|---|---|---|
| 1 | **4a** | $H_2$/CO (7 bar), BIPHEPHOS | -$CO_2$Et, H, H **18**, 67%, >99:1 |
| 2 | **4b** | $H_2$/CO (7 bar), BIPHEPHOS | -$CO_2$*t*-Bu, H, H **19** 56%, 95:5 |
| 3 | **4c** | $H_2$/CO (7 bar), BIPHEPHOS | -$CO_2$*t*-Bu, Me, H, **20**, 58%, 50:50 |
| 4 | **4d** | $H_2$/CO (7 bar), BIPHEPHOS | -$(CH_2)_2$Ph, Me, H **21**, 56%, dr 96 ; 5 |
| 5 | **6** | $H_2$/CO (7 bar), BIPHEPHOS | -$CO_2$*t*-Bu, H, Ph **22**, 15%, 96:4 |
| 6[b] | **6** | $H_2$/CO (7 bar), BIPHEPHOS | **22**, 13%, 92:8 |
| 7 | **6** | $H_2$/CO (7 bar), $(EtO)_3P$ | **22**, 12%, 95:5 |
| 8 | **6** | $H_2$/CO (30 bar), BIPHEPHOS | **22**, 62%, 95:5 |
| 9 | **14** | $H_2$/CO (30 bar), $(EtO)_3P$ | -$(CH_2)_2$Ph, H, Ph **23**, 58%, 96 ; 5 |
| 10 | **15** | $H_2$/CO (30 bar), $(EtO)_3P$ | -$(CH_2)_2$Ph, Me, Ph **24**, 58%, 85:15 |

a) reaction conditions: $H_2$/CO 1 : 1 as in the table, $[Rh(acac)(CO)_2]$ (2 mol%), ligand (4 mol%) as in the table,THF, 70 °C, 12 h. b) Reaction done under MW dielectric heating (70 °C for 2 h.)

To our delight, **4a** and **4b** provided bicyclic products **18** and **19** in satisfactory yield and high diastereoselectivity (Table 2, entry 1-2).[17] The presence of the methyl group did not affect yield and diastereoselectivity in the CHC reaction of **4d** where a Ph-$CH_2CH_2$- chain replaces the *t*-butoxycarbonyl moiety. On the contrary, when compound **4c**, carrying a methyl group in the allyl position, was submitted to the same conditions, product **20** ($R^1$ = Me) was obtained with an acceptable 58% yield but as a 1:1 mixture of diastereomers (Table 2, entry 3). Probably the contemporary presence of an ester in C-2 position and an alkyl group in C-3 position influenced the stability of the chair like intermediates in the CHC reaction. A lower energy difference between the two possible conformations (both having an alternate equatorial/axial disposition of the methyl and *t*-butyl ester group) generates no preference in the attack of the OH group.

With internal alkenes **6**, **14** and **15**, the first hydroformylation is expected to occur with the insertion of the aldehyde onto the benzylic position and to afford exclusively the six-membered ring through OH cyclisation.[23] Effectively, when compound **6** was exposed to the same CHC conditions developed so far, the bicyclic product **22** was obtained as a single product albeit in low yield (Table 2, entry 5). Aiming to improve the reaction, MW dielectric heating was applied and triethylphosphite was employed as the ligand but any progress in the reaction was observed (Table 2, entries 6 and 7). As the main constituent of the crude reaction mixture was unreacted alkene **6**, we decided to increase the syngas pressure up to 30 bars. Under these conditions, product **22** was finally isolated in acceptable yield and excellent 95:5 diastereomeric ratio (Table 2, entry 8). Analogously, **14** was readily transformed into **23** with acceptable yield and high selectivity (Table 2, entry 9). However, when the more hindered compound **14** was submitted to the same conditions applied to **6**, the yield of the CHC product dropped. In this case, the use of triethylphosphite (a less hindered ligand respect to BIPHEPHOS) was necessary in order to obtain product **24** in 85 : 15 dr and with comparable yield respect to **23** (Table 2, entry 10). This result could be related to the contemporary presence of both the methyl group in C-3 and the phenyl moiety in C-5 position. The absolute configuration of the product was established on the basis of X-ray analysis of a crystal derived from compound **22** (Figure 2).

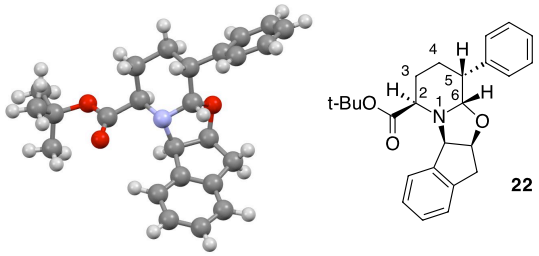
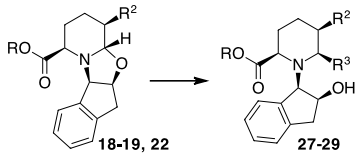


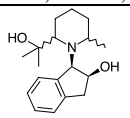
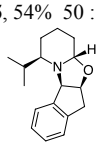
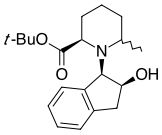
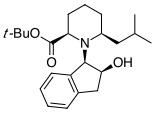
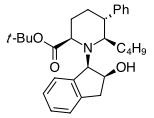

Figure 2. X-ray structure of compund **22**

A *trans* relationship between the hydrogen atoms at C-2 and C-5 was revealed, whereas at the ring junction, the hydrogen at C-6 were *cis* respect to the hydrogen at C-5 and *trans* respect to the hydrogen at C-2 (Figure 2). The relative configuration at C-3 (for compounds **20**, **21** and **24**) was established by NOE experiments. Finally, in order to test the applicability of the proposed protocols for the synthesis of substituted pipecolic acid derivatives, the introduction of the substituent in position 6

and the removal of the chiral auxiliary were attempted on compounds **18**, **19** and **22** (Table 3).

Table 3. Oxazolidine ring opening

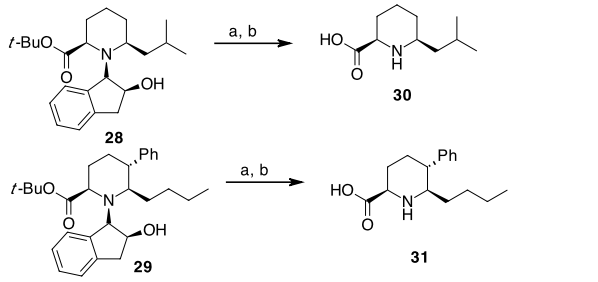



| Entry | sm | Conditions | Product, Yield%, dr |
|---|---|---|---|
| 1 | **18** | MeMgBr, $Et_2O$, r.t. , 30 min or 2 h |  **25**, 54% 50 : 50 |
| 2 | **18** | MeMgBr, $Et_2O$, -78 °C, 30 min[b] |  **26,** 48% [a] |
| 3 | **18** | Zn, allyl bromide, TMSCl, EtOH, 1 h | **18** |
| 4 | **18** | Zn, ethyl bromoacetate, $Et_2O$/toluene 1 h | **18** |
| 5 | **19** | MeMgBr, $Et_2O$, 0 °C, 30 min |  **27**, 79%, 50:50 |
| 7 | **19** | *i*-BuMgBr, $Et_2O$, 0 °C, 30 min |  **28**, 73%, 65:35 |
| 8 | **22** | BuMgBr, $Et_2O$, r.t., 2 h |  **29**, 67%, 75:25 |

a) Stereochemistry not investigated. b) A large excess of MeMgBr (10 eq) was employed. Probably the intermediate OH was transformed into the halogen derivative, further reduced under Grignard reaction conditions.

Initial efforts for promoting the oxazolidine ring-opening on methyl ester **18** were fruitless as the reaction of methyl magnesium iodide gave compounds **25** and **26** derived from attack of the Grignard either on C-6 and the ethyl ester moiety (Table 3, entry 1) and further OH reduction (Table 3, entry 2). Speculating that the hemiaminal carbon (at C-6) would have a reactivity similar to a carbonyl group, **18** was subjected to classic Barbier's conditions with allyl bromide (3 eq.) and Zn(0) (2 eq.) in EtOH for 4 h (Table 3, entry 3). However, this attempt was ineffective, both starting materials being recovered. Repeating the protocol on ethyl bromoacetate in the presence of TMSCl as the activating agent for Zn(0) in a mixture of $Et_2O$/toluene, again no reaction occurred (Table 3, entry 4). However, the more bulky *t*-butyl ester group present in **19** and **22** prevented the nucleophilic attack to the carbonyl in position 2. Treating these compounds with different Grignard reagents, the desired products **28** or **29** were isolated in good yields (Table 3, entry 5-9).[24] Probably the presence of the *t*-butoxycarbonyl group, that can in principle chelate the Mg, may explain the lower selectivity observed on these substrates if compared with the oxazolidine ring opening with substrates carrying an alkyl group in position 2.[17]

Compounds **28** and **29**, after separation from the other diastereoisomers by column chromatography, were submitted to removal of the chiral auxiliary with hydrogen and Pd, followed by *t*-butyl ester hydrolysis in acidic conditions (TFA, Scheme 4).




Scheme 4 *a:* $H_2$ (10 bar), $Pd(OH)_2/C$, MeOH, r.t. 10 h. *b:* TFA, $CH_2Cl_2$, r.t., 4 h.

Compound **30** was obtained in 70% yield over the last two steps (dr 76:24), while a better stereoselectivity (>99:1) with 61% yield was observed on trisubstituted compound **31**.

## Conclusions

Once again the CHC reaction demonstrates to be an useful transformation in the stereoselective synthesis of heterocyclic compounds. A good protocol for the functionalization of 4-pentenoic acid derivatives via Heck reaction followed by CHC was developed obtaining bicyclic products with good yields and excellent selectivity. The final transformation of the CHC products into the corresponding pipecolic acids demonstrates the potential of the protocol proposed. The CHC of internal alkenes still needs further studies especially in term of the diastereoselectivity observed in some C-3 substituted substrates. Moreover, the synthetic scheme proposed permits to access new interesting building blocks not available so far and potentially interesting for the synthesis of new biologically active molecules or organocatalysts.

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## Notes and references

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Electronic Supplementary Information (ESI) available: General experimental procedures and product characterization. See DOI: 10.1039/c000000x/

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