CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200801795

A General Approach to Aza-Heterocycles by Means of Domino Sequences Driven by Hydroformylation

Etienne Airiau,[a] Thomas Spangenberg,[a] Nicolas Girard,[a] Angèle Schoenfelder,[a] Jessica Salvadori,[b] Maurizio Taddei,[b] and André Mann*[a]

Dedicated to Dr. C. Mioskowski

Abstract: The development of hydroformylative domino reactions of easily accessible vinyl acetamides is described. Extremely regioselective hydroformylation of terminal double bounds provides a transient *N*-acyliminium that can be trapped by various nucleophiles to give several aza-heterocylic scaffolds in a diastereoselective manner.

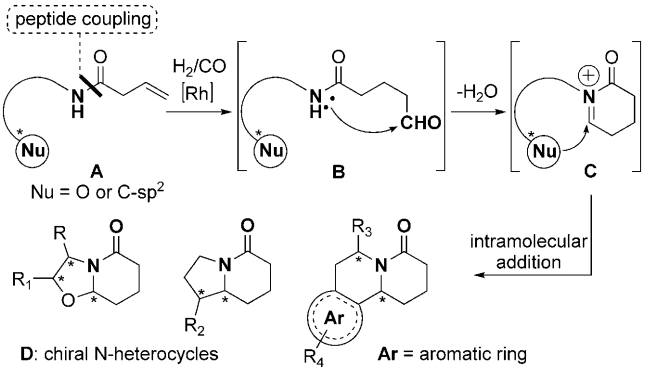
Keywords: cyclohydrocarbonylation · diastereoselectivity · domino reactions · heterocycles · hydroformylation

Introduction

The sequence of forming successively two or more new chemical bonds in a single transformation without the isolation of the intermediate has been defined as a domino sequence.[1–4] Originally fuelled by the quest of step- and atom-economy in the syntheses of complex targets from natural sources,[5–7] domino reactions have found large applications in the synthesis of new cyclic or heterocyclic structures from open-chain substrates.[8] The optimal design of domino reactions should deliver complex compounds starting from easily available reagents and implementing simple reactions.

Hydroformylation of alkenes is a powerful example of efficient C–C bond formation.[9–12] This reaction, by carbon activation, introduces an aldehyde onto a double bond, providing a new functional group suitable for multistep sequences. The application of hydroformylation in domino processes has been investigated as a strategy to prepare different heterocycles, and several creative applications have been reported.[13–17]

Based on our previous experiences in the preparation of aldehydes by hydroformylation,[18–19] we ambitioned to expand the concept of carbonylative-based domino reactions[20] in designing new synthetic routes. In this work, a general approach to aza-heterocycles by domino sequences driven by hydroformylation is disclosed. Our strategy is illustrated in Scheme 1: the key substrate (**A**) features a terminal double bond and a nucleophile linked through an amide group working itself as an additional nucleophile. Indeed, upon hydroformylation, the amide NH will react with the newly formed aldehyde yielding a highly activated *N*-acyliminium ion **C**.[21–22] Then, a second nucleophilic attack, completing the sequence of the domino cyclohydrocarbonylation (CHC)[14b] delivers the final polycyclic products **D**. The structure of the products obtained with this strategy will be subordinated to the nature of the three reactive centers (vinyl, amide, and nucleophile) and their relative locations.



Scheme 1. The hydroformylation of linear vinylacetamides (**A**) to terminal aldehydes (**B**) is triggering domino reactions with appended nucleophiles (**Nu**) via a transient *N*-acyliminium (**C**) towards complex heterocycles (**D**).

Results and Discussion

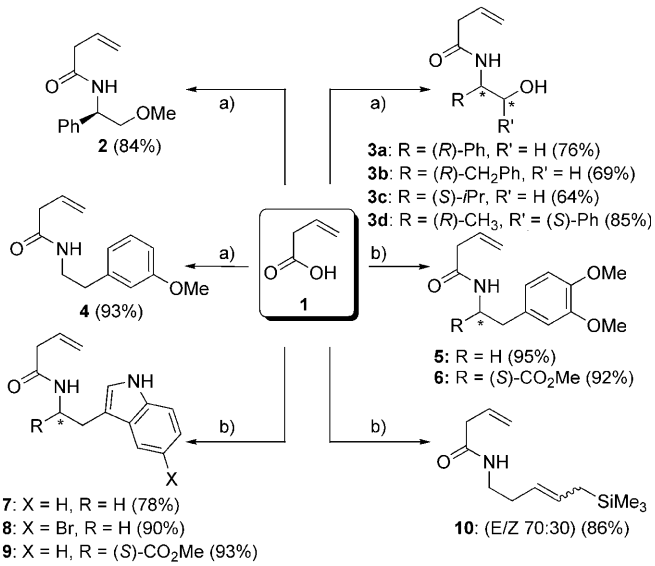
The starting substrates were easily prepared by a one-step coupling reaction between 3-butenoic acid (**1**) and several amines (Scheme 2). Indeed by using different chiral amino alcohols, products **3a–d** were obtained with an OH as second nucleophile suitable for cyclization to give bicyclic oxazole derivatives. When phenethylamine derivatives, tryptamine or tryptophan methyl ester were coupled with **1**, compounds **4–9** were produced as ideal substrates for domino CHC Pictet–Spengler reactions. Finally the amide **10** derived from 5-bromopent-2-enyltrimethylsilane was employed to test the feasibility of a domino CHC/aza-Sakurai–Hosomi reaction.

Initially, the optimization work was done by using compound **2**. All the possible products (**11–16**) that can be formed during the hydroformylation of **2** are reported in Table 1. As the clean generation of the linear aldehyde **11** by hydroformylation is crucial for the domino sequence, different variables, such as the solvent, the ligand for Rh^I, the temperature, acid additives, and the nature of the conditions needed for the domino sequence were addressed. The ratios of **11–16** were easily quantified by ^1H NMR spectroscopy and the data are summarized in Table 1.

[a] E. Airiau, T. Spangenberg, Dr. N. Girard, A. Schoenfelder, Dr. A. Mann
Faculté de Pharmacie, Université Louis Pasteur de Strasbourg
Laboratoire de Pharmacochimie de la Communication Cellulaire
UMR 7175/LC1, 74, route du Rhin
BP 60024, 67401 Illkirch (France)
Fax: (+33) 390-244-310
E-mail: andre.mann@pharma.u-strasbg.fr

[b] J. Salvadori, Prof. M. Taddei
Dipartimento Farmaco Chimico Tecnologico
Università degli Studi di Siena
Via A. Moro 2, 53100 Siena (Italy)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801795.



Scheme 2. General procedure for peptide couplings: a) **1**, DCC, HOBt, CH_2Cl_2, RT, 24 h; b) **1**, EDC, HOBt, CH_2Cl_2, RT, 24 h; Substrates for peptide couplings: (1*R*)-2-methoxy-1-phenylethanamine **32** for **2**, (*R*)-(−)-2-amino-2-phenylethanol for **3a**, (*R*)-2-amino-3-phenyl-1-propanol for **3b**, (*S*)-(+)-2-amino-3-methyl-1-butanol for **3c**, D-(+)-norephedrine for **3d**, 2-(3-methoxyphenyl)ethylamine for **4**, 2-(3,4-dimethoxyphenyl)-ethylamine for **5**, (*S*)-methyl 2-amino-3-(3,4-dimethoxyphenyl)propanoate **33** for **6**, tryptamine for **7**, 5-bromotryptamine for **8**, (*S*)-methyl 2-amino-3-(1*H*-indol-3-yl)propanoate **34** for **9**, and 5-(trimethylsilyl)pent-3-en-1-amine **36** for **10**. DCC= *N*,*N*′-dicyclohexylcarbodiimide; EDC=*N*′-(3-dimethylaminopropyl)-*N*-ethyl-carbodiimide; HOBt=1-hydroxybenzotriazole.

The syngas (H_2/CO 1:1) pressure was fixed at 5 bar and [Rh(acac)$(CO)_2$] was chosen as the precatalyst.[9] All the ligands (PPh_3 (**17**), xantphos (**18**), 6-DPPon (**19**),[23] biphephos (**20**))[24,25] produced full conversions to linear or branched aldehydes **11** or **12**, with some amounts of the fully reduced adduct **13** (Table 1, entries 1–4). As expected, the bulky diphosphite biphephos favored the formation of the linear aldehyde, whereas xantphos, PPh_3, or 6-DPPon gave higher amounts of the branched aldehyde.

Next, the influence of Brønsted or Lewis acids (*p*TSA, PPTS, BF_3·Et_2O, and $Zn(OTf)_2$) were examined. The stability of biphephos in acidic media was questionable as a water molecule will be released during the cyclohydrocarbonylation step. Interestingly, no notable changes were detected in the conversion balance (Table 1, entries 5–10), except that now the major adducts are enamides **15** or **16**, and the chemistry went a step forward. The transient aminals, derived from aldehydes **11** and **12**, respectively, underwent dehydration to enamides **15** and **16**, which, in this particular case, results from further π-isomerization. The stability of our catalytic system (Rh^I and biphephos) was proved by ^{31}P NMR spectroscopic experiments.[26] Moreover, biphephos, either in THF, toluene, or CH_2Cl_2 favors the formation of linear aldehyde (Table 1, entries 5, 6, and 7). A point to note is that at room temperature the major pathway is the conversion of **2** to **14** by double-bond isomerization (entry 11), as a result of a rhodium hydride addition–elimination. But at 70 °C, the catalytic cycle is set for hydroformylation: the linear aldehyde **11** is produced as the major adduct, and the corresponding branched aldehyde **12** is the minor one. These results suggest that, at 70 °C, the presence of electron-rich heteroatoms (N, O) in substrate **2** does neither compete with the complexation of biphephos to Rh^I nor to the ligation of the alkene. Thus, biphephos was selected as the ligand of choice in further experiments.

From this prelude, it appears that the optimal hydroformylation conditions of **2** are achieved by using biphephos as the ligand for Rh^I in THF at 70 °C and that the presence of acid additives does not compromise the Rh^I-promoted catalytic cycle.

The application of these conditions to amide **3a** with acid additives gave similar results and the oxazolopiperidone **21a** was obtained as a mixture of two diastereomers (**21a**/**21a′** 91:9) separable by chromatography (Table 2, entry 1).

This result confirmed that the linear hydroformylation was the predominant pathway in the domino cyclohydrocarbonylation. The main diastereomer was identified as the *trans* adduct by comparison with reported data.[27,28] Indeed, compound **21a** (*trans* adduct) has already been prepared by different routes. Furthermore, the reactivity of the latent iminium in **21a** to various organometallic reagents was used towards the synthesis of natural compounds. According to Bosch,[28] the *trans* diastereomer is the most valuable for further chemical transformations.

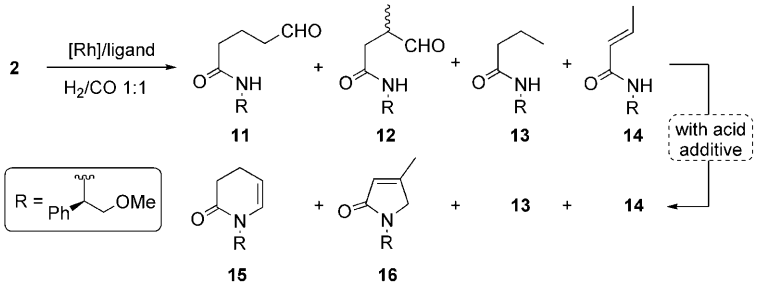
This seminal example of a hydroformylation-based domino reaction proved to be of general use, as oxazolopiperidones derived from phenylalaninol **3b**, valinol **3c**, and norephedrine **3d** were converted into bicyclic **21b**–**21b′**, **21c**–**21c′**, and **21d**–**21d′** adducts in good yields with comparable diastereoselectivities (ca. 90:10).

Our approach towards the oxazolopiperidones **21a**–**d** has some advantages relative to the existing methods as the essential aldehyde function is generated in situ from an inexpensive alkene **1**. As many other similar alkenes are available from the feedstock, extensions of this domino CHC/heteroatoms addition are conceivable.

Next, we decided to examine if an electron-rich aromatic ring could be used as the nucleophile partner in a domino CHC/Pictet–Spengler sequence.[29] Phenethylamine derivatives (Table 3) and indole derivatives (Table 4) were prepared for that purpose and submitted to the standard hydroformylative conditions in presence of Brønsted or Lewis acids.

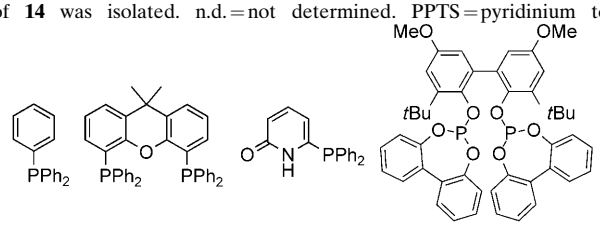
The expected adducts **22**–**27** were isolated in good to very good yields. They result from a linear hydroformylation of **4**–**9** and a subsequent quenching of the transient *N*-acyliminium with the electron-rich aromatic ring. Depending on the substrates, various quantities of acid additives were necessary to obtain good yields. The domino CHC/Pictet–Spengler reaction works well with Brønsted or Lewis acid (Table 3, entries 1–6) and provides benzo[*a*]quinolizidine-type products in very good yields and with good diastereoselectivity for **24**. With indole derivatives **7** and **8**, BF_3·Et_2O gave better results (Table 4, entries 1–4) and indoloquinolizidines

Table 1. Optimization of the experimental conditions for the hydroformylation of **2**.[a]



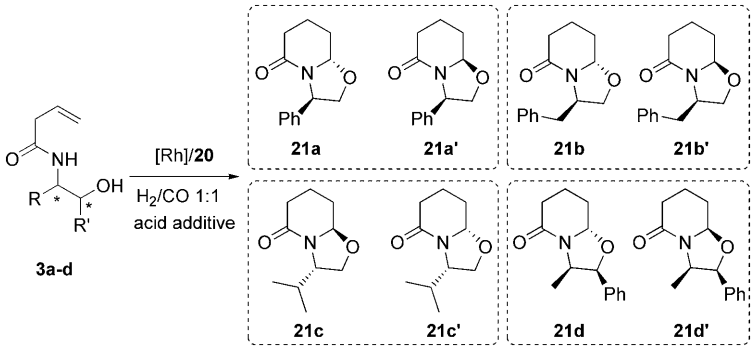
Entry	Additive (10 mol%)	Ligand	Hydroformylation ([%])	Regioselectivity
1	–	**17**	**11**+**12** (95)	**11/12** 67:33
2	–	**18**	**11**+**12** (94)	**11/12** 72:28
3	–	**19**	**11**+**12** (95)	**11/12** 67:33
4	–	**20**	**11**+**12** (93)	**11/12** 92:8
5	*p*TSA	**20**	**15**+**16** (94)	**15/16** 96:4
6[b]	*p*TSA	**20**	**15**+**16** (90)	**15/16** 91:9
7[c]	*p*TSA	**20**	**15**+**16** (85)	**15/16** 86:14
8	PPTS	**20**	**15**+**16** (93)	**15/16** 96:4
9	BF_3·Et_2O	**20**	**15**+**16** (94)	**15/16** 96:4
10	$Zn(OTf)_2$	**20**	**15**+**16** (94)	**15/16** 96:4
11[d]	*p*TSA	**20**	**15**+**16** (15)[e]	n.d.

[a] [$Rh(CO)_2$acac]/ligand/**2** 1:2:50, [**2**] = 0.04 M, THF (3 mL), 5 bar H_2/CO 1:1, 70 °C, 12 h. Ratios were determined by ^{1}H NMR spectroscopic analysis on the crude reaction mixtures. Full conversion was observed in each case [b] Reaction in toluene. [c] Reaction in CH_2Cl_2 at 50 °C. [d] Reaction at room temperature. [e] 85% of **14** was isolated. n.d. = not determined. PPTS = pyridinium tosylate; *p*TSA = *p*-toluenesulfonic acid.



TPP (**17**) xantphos (**18**) 6-DPPon (**19**) biphephos (**20**)

Table 2. Domino CHC/hetero nucleophilic addition on **3a–d**.[a]



Entry	Substrate	Additive [mol%]	Yield [%][b]	Products (*trans*/*cis*)
1	**3a**	*p*TSA (10)	94	**21a**/**a′** 91:9
2	**3b**	*p*TSA (10)	90	**21b**/**b′** 90:10
3	**3c**	*p*TSA (10)	78	**21c**/**c′** 91:9
4	**3d**	PPTS (5)	91	**21d**/**d′** 86:14

[a] [Rh(acac)$(CO)_2$]/**20**/**3a–d** 1:2:100, [**3a–d**] = 0.04 M, THF, 5 bar H_2/CO 1:1, 70 °C, 12 h. [b] Isolated yield. acac = acetylacetonate.

25 and **26** were obtained with 85 and 73% yields, respectively. Surprisingly, with tryptophan methyl ester derivative **9**, the nature of the acid additive has a great influence on the diastereoselectivity of the reaction.

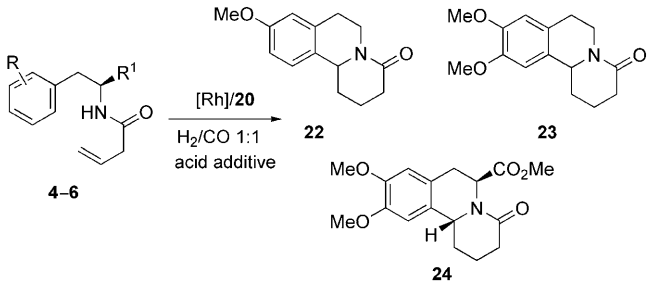
Indeed, in presence of *p*TSA (Table 4, entry 5), a mixture of **27** and **27′**, separable by chromatography, was obtained with 95% yield with a good diastereoselectivity (88:12: the configuration of the major diastereomer was confirmed by X-ray diffraction analysis[30]). Whereas, with BF_3·Et_2O (entry 6), a 1:1 mixture of the two diastereomers was obtained.[31] As expected, the in situ formation of the linear aldehyde gave the domino sequence CHC/Pictet–Spengler reaction, allowing a very straightforward access to N-containing polycyclic compounds starting from carefully designed starting materials. To the best of our knowledge, this represents the first application of a domino CHC/Pictet–Spengler reaction applied to electron-rich aromatic rings or indoles nucleus.

Finally, we decided to investigate the nucleophilic reactivity of allylsilane in the context of cyclohydrocarbonylation. For that purpose, we prepared substrate **10** in four steps passing through bromallylsilane **28** by cross-metathesis (Scheme 3).[32]

We expected that a chemoselective hydroformylation would operate to produce the linear aldehyde leaving intact the double bound of the allylsilane. Then, the CHC to the amidic nitrogen atom should produce an *N*-acyliminium ready for an aza-Sakurai–Hosomi reaction. The newly formed vinyl alkene **30** could be again hydroformylated regioselectively to produce the terminal aldehyde in adduct **31** (Scheme 3).

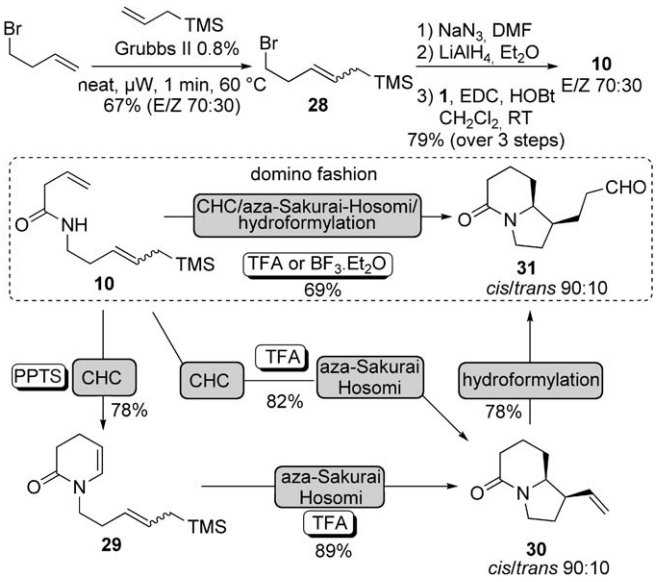
Thus several conditions were tested (Table 5). Depending on the solvent and the acid additives, three different adducts **29**, **30**, and **31**, corresponding to each singular step could be isolated. Enamide **29** (entry 1) is obtained in 78% yield in

Table 3. Domino CHC/Pictet–Spengler reaction on **4–6**.[a]



Entry	Substrate	Additive [mol%]	Product	Yield [%][b]
1	**4**	*p*TSA (50)	**22**	90
2	**4**	BF_3·Et_2O (20)	**22**	85
3	**5**	*p*TSA (20)	**23**	88
4	**5**	BF_3·Et_2O (20)	**23**	95
5	**6**	*p*TSA (10)	**24**	67[c]
6	**6**	BF_3·Et_2O (10)	**24**	84[c]

[a] [Rh(acac)$(CO)_2$]/**20**/**4–6** 1:2:100, [**4–6**] = 0.04 M, THF, 5 bar H_2/CO 1:1, 70 °C, 12 h. [b] Isolated yield. [c] Only one diastereomer was isolated.



Scheme 3. Access to indolizinones by means of CHC/aza-Sakurai–Hosomi/hydroformylation.

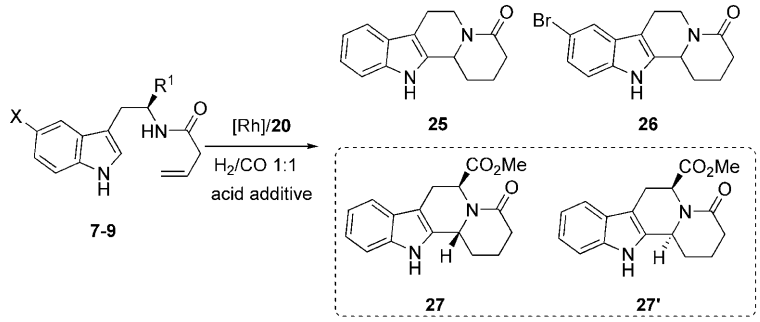
THF with PPTS (5 mol%), which establishes that the hydroformylation is selective for the terminal double bound. No hydroformylation of the internal alkene (allylsilane) was observed, that left room for the subsequent aza-Sakurai–Hosomi reaction.

When compound **29** was isolated and treated with four equivalents of trifluoroacetic acid (TFA) in CH_2Cl_2, adducts **30** were obtained as a mixture of two diastereomers (*cis*/*trans* 90:10) in 89% yield.[33] It was also possible to isolate **30** in a one-pot operation if the hydroformylation was carried out without acid additive, and after the autoclave had been cooled and degassed, TFA was added at room temperature to give **30** in 82% yield (entry 2) with the same diastereoselectivity. Then, hydroformylation of **30** in classical conditions (without acid additive) gave **31** with 78% yield.

Now, we decided to produce **31** in a domino reaction. When allylsilane **10** was mixed in CH_2Cl_2 with one equivalent of TFA and submitted to hydroformylation conditions, after 12 h at 55 °C, adduct **31** could be isolated in 63% yield (entry 3). Use of a Lewis acid additive in CH_2Cl_2 (entry 4) does not improve the yield of the reaction. The best result was obtained by using 0.5 equivalents of BF_3·Et_2O in THF (entry 5) to give **31** with 69% yield as a mixture of two diastereomers (*cis*/*trans* 90:10).

This result confirms that four reactions were involved in the domino sequence involving selective hydroformylation of the terminal alkene, cyclization, aza-Sakurai–Hosomi reaction on the transient *N*-acyliminium, and a final regioselective hydroformylation. In this sequence, from the linear adduct **10**, two cycles and nine new bounds are formed in the same chemical operation. A domino sequence that included hydroformylation was described by Hoffmann in which an allylborane was involved.[8] The advantage of the process depicted in Scheme 3 is a straightforward access to the allylsilane derivative **10**. Additionally, upon certain reaction conditions, compounds **29**, **30**, and **31** can be obtained separately allowing further potential transformations into biomolecules. We believe that the elaboration of other allylsilanes for the

Table 4. Domino CHC/Pictet–Spengler reaction on **7–9**.[a]



Entry	Substrate	Additive [mol%]	Product	Yield [%][b]
1	**7**	*p*TSA (10)	**25**	66
2	**7**	BF_3·Et_2O (10)	**25**	85
3	**8**	*p*TSA (20)	**26**	70
4	**8**	BF_3·Et_2O (10)	**26**	73
5	**9**	*p*TSA (10)	**27**+**27′**	95[c]
6	**9**	BF_3·Et_2O (10)	**27**+**27′**	85[d]

[a] [Rh(acac)$(CO)_2$]/**20**/**7–9** 1:2:100, [**7–9**] = 0.04 M, THF, 5 bar H_2/CO 1:1, 70 °C, 12 h. [b] Isolated yield. [c] **27**/**27′** 88:12; the structure of **27** was confirmed by X-ray diffraction analysis.[30d] **27**/**27′** 54:46.

Table 5. Domino CHC/aza-Sakurai–Hosomi/hydroformylation on **10**.[a]

Entry	Solvent (T [°C])	Additive [equiv]	Product	Yield [%][b]
1	THF (70)	PPTS (0.05)	**29**	78
2	CH_2Cl_2 (55)	TFA (1)	**30**	82[c]
3	CH_2Cl_2 (55)	TFA (1)	**31**	63
4	CH_2Cl_2 (55)	BF_3·Et_2O (0.5)	**31**	61
5	THF (70)	BF_3·Et_2O (0.5)	**31**	69

[a] [Rh(acac)$(CO)_2$]/**20**/**10** 1:2:100, [**10**] = 0.04 M, 5 bar H_2/CO 1:1, 12 h. *cis*/*trans* ratios were 90:10 in all cases. Determined by ^{1}H NMR spectroscopy for **30** and GCMS analyses for **31**. [b] Isolated yield. [c] Reaction for 4 h, then TFA (1 equiv), 12 h, RT.

domino cyclohydrocarbonylation/aza-Sakurai–Hosomi/hydroformylation may lead to series of analogues of **29**, **30**, or **31**.

Conclusion

We have developed new domino reactions for the synthesis of aza-heterocycles by using hydroformylation as the trigger. Our strategy allows full control over product formation: by fine-tuning of the reaction conditions, various heterocycles can be obtained from simple, readily available materials from the feedstock. Moreover, complex, aza-polycyclic systems can be efficiently built in a diastereoselective fashion. Our present work has shown that domino reactions based on hydroformylation have a great potential in organic synthesis, the combination of Rh^I and biphephos is ideal for linear hydroformylation even in the presence of multiple components in the reaction mixture. Work is in progress by our group to experiment with other domino sequences in association with the hydroformylation reaction.

Experimental Section

General: All reagents were used as purchased from commercial suppliers without further purification. The reactions were carried out in oven-dried or flamed vessels and performed under argon. Solvents were dried and purified by conventional methods prior use. Et_2O and THF were freshly distilled from sodium/benzophenone and dichloromethane was distilled from CaH_2. Toluene was distilled from sodium. Flash column chromatography was performed with Merck silica gel 60, 0.040–0.063 mm (230–400 mesh). Merck aluminum-backed plates pre-coated with silica gel 60 (UV_{254}) were used for TLC and were visualized by staining with $KMnO_4$. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker (300/75/121 MHz) or (200/50/81 MHz) spectrometers. Conditions are specified for each spectrum (temperature 25 °C unless specified). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; sext, sextuplet; br, broad. Chemical shifts (δ) are given in ppm relative to the resonance of their respective residual solvent peak, $CHCl_3$ (^{1}H: δ = 7.27, ^{13}C: 77.16 ppm, the middle peak). IR spectra were taken with a Nicolet 380 FTIR spectrometer. HR and LRMS analyses were conducted by the Institut Fédératif de Recherche 85 at the Louis Pasteur University, Strasbourg. Melting points were determined on a Büchi Melting Point B-540 apparatus in open capillary tubes and are uncorrected. Specific rotations were measured with a Perkin–Elmer apparatus by using a 10 cm cell with a Na 589 nm filter: values are given in 10^{-1} °cm^2 g^{-1}.

General procedure A for the formation of products 2–10: But-3-enoic acid (1 equiv) was added to a solution of the desired substrate (1 equiv) in anhydrous CH_2Cl_2 (0.3 M) in an ice bath. Then, DCC (1.05 equiv, for compounds **2**, **3a**, **3b**, **3c**, **3d**, and **4**) or EDC (1.1 equiv, for compounds **5**, **6**, **7**, **8**, **9**, and **10**) and HOBt (1 equiv) were added and the solution was stirred at room temperature for 24 h. The suspension was filtered off and the organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4), filtered, and concentrated to give a yellow oil.

General procedure B for hydroformylation: In a stainless steel autoclave under an inert atmosphere, a solution of dicarbonylacetylacetonato rhodium (1 mol %) and biphephos (2 mol %) in anhydrous degassed solvent (3 mL), prepared in a Schlenk glassware under inert atmosphere, was added to a solution of the desired olefin (1 equiv) and acid if necessary in anhydrous degassed solvent to reach a final concentration of 0.04 M. The autoclave was flushed with H_2/CO (1:1) three times. Then, the autoclave was filled with 5 atm. of H_2/CO (1:1) and was heated at the desired temperature with stirring for 12 h. Then, the autoclave was cooled to room temperature and gases were slowly and carefully released. The reaction mixture was then concentrated under reduced pressure to give an oil. The residue was purified by flash chromatography.

***N*-[(1*R*)-2-Methoxy-1-phenylethyl]but-3-enamide (2)**: Compound **2** was prepared by following the general procedure A as described above from **32** (1.88 g, 12.4 mmol). The residue was purified by flash chromatography (70:30 to 60:40 pentane/EtOAc) to give **2** as a white solid (2.29 g, 84 %). $[\alpha]_D^{20} = -30.1$ (c = 1.0 in $CHCl_3$); m.p. 39–40 °C; IR (neat): $\tilde{\nu}$ = 3297, 2871, 1640, 1537 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.35–7.25 (m, 5H), 6.36 (br d, J = 7.7 Hz, 1H), 5.97 (m, 1H), 5.28 (m, 1H), 5.22 (m, 1H), 5.17 (dt, J = 7.8, 4.7 Hz, 1H), 3.65 (d, J = 4.7 Hz, 2H), 3.35 (s, 3H), 3.06 ppm (dt, J = 7.0, 1.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.1 (C), 139.9 (C), 131.4 (CH), 128.6 (CH), 127.6 (CH), 126.8 (CH), 119.8 (CH_2), 75.0 (CH_2), 59.2 (CH_3), 52.6 (CH), 41.7 ppm (CH_2); HRMS-ESI: m/z: calcd: 220.1332 $[M+H]^+$; found: 220.1332 (Δ = 0.2 ppm).

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]but-3-enamide (3a)**: Compound **3a** was prepared by following the general procedure A as described above from (*R*)-(−)-2-amino-2-phenylethanol (1.00 g, 7.29 mmol). The residue was purified by flash chromatography (98:2 CH_2Cl_2/MeOH) to give **3a** as a white solid (1.14 g, 76 %). $[\alpha]_D^{20} = -42.1$ (c = 1.0 in $CHCl_3$); m.p. 105–106 °C; IR (neat): $\tilde{\nu}$ = 3307, 1644, 1632, 1493, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.45–7.26 (m, 5H), 6.39 (br d, J = 7.2 Hz, 1H), 6.10–5.89 (m, 1H), 5.32–5.23 (m, 2H), 5.09 (dt, J = 7.2, 4.7 Hz, 1H), 3.90 (d, J = 4.7 Hz, 2H), 3.1 (dt, J = 7.2, 1.1 Hz, 2H), 2.52 ppm (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.4 (C), 139.1 (C), 131.2 (CH), 129.0 (CH), 127.9 (CH), 126.7 (CH), 120.0 (CH_2), 66.3 (CH_2), 55.9 (CH), 41.5 ppm (CH_2); HRMS-ESI: m/z: calcd: 206.1176 $[M+H]^+$; found: 206.1175 (Δ = 0.2 ppm).

***N*-[(2*R*)-1-Hydroxy-3-phenylpropan-2-yl]but-3-enamide (3b)**: Compound **3b** was prepared by following the general procedure A as described above from (*R*)-2-amino-3-phenyl-1-propanol (800 mg, 5.29 mmol). The residue was purified by flash chromatography (98:2 CH_2Cl_2/MeOH) to give **3b** as a white solid (798 mg, 69 %). $[\alpha]_D^{20} = +33.8$ (c = 1.0 in $CHCl_3$); m.p. 69–70 °C; IR (neat): $\tilde{\nu}$ = 3286, 1645, 1549, 1450, 1428 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.37–7.21 (m, 5H), 6.02 (br d, J = 7.4 Hz, 1H), 5.96–5.75 (m, 1H), 5.24–5.12 (m, 2H), 4.26–4.10 (m, 1H), 3.70 (dd, J = 11.0, 3.7 Hz, 1H), 3.60 (dd, J = 11.0, 5.1 Hz, 1H), 3.24 (br s, 1H), 2.98 (br d, J = 7.1 Hz, 2H), 2.90 ppm (dd, J = 7.3, 3.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 171.4 (C), 137.6 (C), 131.1 (CH), 129.4 (CH), 128.7 (CH), 126.8 (CH), 120.1 (CH_2), 64.1 (CH_2), 53.1 (CH), 41.7 (CH_2), 37.0 ppm (CH_2); HRMS-ESI: m/z: calcd: 220.1332 $[M+H]^+$; found: 220.1328 (Δ = 2.0 ppm).

***N*-[(2*S*)-1-Hydroxy-3-methylbutan-2-yl]but-3-enamide (3c)**: Compound **3c** was prepared by following the general procedure A as described above from (*S*)-(+)-2-amino-3-methyl-1-butanol (300 mg, 2.91 mmol). The residue was purified by flash chromatography (98:2 CH_2Cl_2/MeOH) to give **3c** as a yellow oil (318 mg, 64 %). $[\alpha]_D^{20} = -50.0$ (c = 1.0 in $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3292, 2960, 1632, 1545 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.02–5.85 (m, 2H), 5.24–5.18 (m, 2H), 3.72–3.58 (m, 4H), 3.02 (br d, J = 7.0 Hz, 2H), 1.92–1.81 (m, 1H), 0.93 (d, J = 6.8 Hz, 3H), 0.89 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.8 (C), 131.4 (CH), 120.0 (CH_2), 63.7 (CH_2), 57.2 (CH), 41.8 (CH_2), 29.1 (CH), 19.6 (CH_3), 18.8 ppm (CH_3); LRMS-ESI: m/z: 194 $[M+Na]$, HRMS-ESI: m/z: calcd: 172.1332 $[M+H]^+$; found: 172.1328 (Δ = 2.4 ppm).

***N*-[(1*R*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]but-3-enamide (3d)**: Compound **3d** was prepared by following the general procedure A as described above from D-(+)-norephedrine (500 mg, 2.66 mmol). The residue was purified by flash chromatography (98:2 CH_2Cl_2/MeOH) to give **3d** as a white solid (497 mg, 85%). $[\alpha]_D^{20} = +88.4$ ($c = 1.0$ in $CHCl_3$); m.p. 78–79°C; IR (neat): 3304, 2921, 2850, 1646, 1540 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.34$–7.27 (m, 5H), 5.89 (ddt, $J = 17.2$, 10.5, 7.0 Hz, 1H), 5.88 (brs, 1H), 5.23–5.16 (m, 2H), 4.83 (d, $J = 3.0$ Hz, 1H), 4.29 (dqd, $J = 8.2$, 6.9, 2.9 Hz, 1H), 3.77 (brs, 1H), 2.99 (dt, $J = 7.1$, 1.2 Hz, 2H), 0.99 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171,4 (C), 140.8 (C), 131.2 (CH), 128.3 (CH), 127.6 (CH), 126.4 (CH), 120.0 (CH_2), 76.5 (CH), 51.1 (CH), 41.6 (CH_2), 14.6 ppm (CH_3); HRMS-ESI: m/z: calcd: 226.1414 $[M+Li]^+$; found: 226.1415 ($\Delta = 0.6$ ppm).

***N*-[2-(3-Methoxyphenyl)ethyl]but-3-enamide (4)**: Compound **4** was prepared by following the general procedure A as described above from 2-(3-methoxyphenyl)-ethylamine (500 mg, 3.31 mmol). The residue was purified by flash chromatography (60:40 to 50:50 pentane/EtOAc) to give **4** as a white solid (677 mg, 93%). M.p. 40–41°C; IR (neat): $\tilde{\nu} = 3249$, 3077, 2942, 1637, 1553, 1486 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.25$–7.20 (m, 1H), 6.79–6.72 (m, 3H), 5.87 (ddt, $J = 17.0$, 10.3, 7.2 Hz, 1H), 5.73 (brs, 1H), 5.21–5.13 (m, 2H), 3.79 (s, 3H), 3.50 (dt, $J = 6.6$, 6.6 Hz, 2H), 2.96 (dt, $J = 7.0$, 1.1 Hz, 2H), 2.78 ppm (t, $J = 7.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 170.6$ (C), 159.9 (C), 140.5 (C), 131.4 (CH), 129.7 (CH), 121.2 (CH), 119.8 (CH_2), 114.5 (CH), 112.0 (CH), 55.3 (CH_3), 41.7 (CH_2), 40.7 (CH_2), 35.8 ppm (CH_2); HRMS-ESI: m/z: calcd: 220.1332 $[M+H]^+$; found: 220.1336 ($\Delta = 1.8$ ppm).

***N*-(3,4-Dimethoxyphenethyl)but-3-enamide (5)**: Compound **5** was prepared by following the general procedure A as described above from 2-(3,4-dimethoxyphenyl)ethylamine (400 mg, 2.21 mmol). The residue was purified by flash chromatography (50:50 pentane/EtOAc) to give **5** as a yellow solid (522 mg, 95%). M.p. 75–76°C; IR (neat): $\tilde{\nu} = 3246$, 3077, 2938, 1633, 1568, 1512, 1256, 1136, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 6.81$–6.77 (m, 1H), 6.72–6.69 (m, 2H), 5.87 (ddt, $J = 16.8$, 10.3, 7.3 Hz, 1H), 5.74 (brs, 1H), 5.20–5.10 (m, 2H), 3.84 (s, 6H), 3.47 (td, $J = 7.0$, 5.8 Hz, 2H), 2.95 (dt, $J = 7.0$, 1.3 Hz, 2H), 2.74 ppm (t, $J = 7.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 170.6$ (C), 149.1 (C), 147.8 (C), 131.4 (CH), 131.3 (C), 120.7 (CH), 119.7 (CH_2), 112.0 (CH), 111.5 (CH), 56.0 (CH_3), 41.7 (CH_2), 40.9 (CH_2), 35.3 ppm (CH_2); HRMS-ESI: m/z: calcd: 250.1438 $[M+H]^+$; found: 250.1431 ($\Delta = 2.8$ ppm).

(*S*)-Methyl 2-(but-3-enamido)-3-(3,4-dimethoxyphenyl)propanoate (6): Compound **6** was prepared by following the general procedure A as described above from **33** (634 mg, 2.65 mmol). The residue was purified by flash chromatography (50:50 pentane/EtOAc) to give **6** as a white solid (749 mg, 92%). $[\alpha]_D^{20} = +69.2$ ($c = 1.0$ in $CHCl_3$); m.p. 122–123°C; IR (neat): $\tilde{\nu} = 3311$, 1748, 1642, 1540, 1521, 1270, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 6.80$–6.76 (m, 1H), 6.64–6.60 (m, 2H), 6.05 (brd, $J = 7.4$ Hz, 1H), 5.89 (ddt, $J = 16.7$, 10.6, 7.1 Hz, 1H), 5.25–5.15 (m, 2H), 4.85 (dt, $J = 7.8$, 5.8 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.73 (s, 3H), 3.07 (brd, $J = 5.8$ Hz, 2H), 3.01 ppm (dt, $J = 7.1$, 1.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 172.1$ (C), 170.1 (C), 149.0 (C), 148.2 (C), 130.9 (CH), 128.2 (C), 121.4 (CH), 120.0 (CH_2), 112.4 (CH), 111.3 (CH), 55.92 (CH_3), 55.89 (CH_3), 53.2 (CH), 52.4 (CH_3), 41.5 (CH_2), 37.5 ppm (CH_2); HRMS-ESI: m/z: calcd: 308.1492 $[M+H]^+$; found: 308.1489 ($\Delta = 1.1$ ppm).

***N*-[2-(1*H*-Indol-3-yl)ethyl]but-3-enamide (7)**: Compound **7** was prepared by following the general procedure A as described above from tryptamine (753 mg, 4.70 mmol). The residue was purified by flash chromatography (60:40 to 50:50 pentane/EtOAc) to give **7** as an off-white solid (843 mg, 78%). M.p. 68–69°C; IR (neat): $\tilde{\nu} = 3384$, 3254, 3081, 1633, 1557, 1455, 1341, 1217 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.37 (brs, 1H), 7.61 (d, $J = 7.9$ Hz, 1H), 7.39 (d, $J = 7.9$ Hz, 1H), 7.25–7.11 (m, 2H), 7.02 (d, $J = 2.2$ Hz, 1H), 5.87 (ddt, $J = 16.9$, 10.3, 7.2 Hz, 1H), 5.75 (brs, 1H), 5.18–5.11 (m, 2H), 3.60 (dt, $J = 6.6$, 6.5 Hz, 2H), 3.00–2.95 ppm (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.7 (C), 136.5 (C), 131.4 (CH), 127.4 (C), 122.24 (CH), 122.20 (CH), 119.8 (CH_2), 119.5 (CH), 118.8 (CH), 112.9 (C), 111.4 (CH), 41.8 (CH_2), 40.0 (CH_2), 25.3 ppm (CH_2); HRMS-ESI: m/z: calcd: 229.1335 $[M+H]^+$; found: 229.1338 ($\Delta = 1.1$ ppm).

***N*-[2-(5-Bromo-1*H*-indol-3-yl)ethyl]but-3-enamide (8)**: Compound **8** was prepared by following the general procedure A as described above from 5-bromotryptamine (300 mg, 1.25 mmol). The residue was purified by flash chromatography (50:50 pentane/EtOAc) to give **8** as a white solid (347, 90%). M.p. 104–105°C; IR (neat): $\tilde{\nu} = 3277$, 1618, 1560, 1436, 1188 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 8.42$ (brs, 1H), 7.71 (d, $J = 1.1$ Hz, 1H), 7.30–7.23 (m, 2H), 7.02 (d, $J = 1.5$ Hz, 1H), 5.86 (ddt, $J = 17.3$, 10.0, 7.1 Hz, 1H), 5.77 (brs, 1H), 5.20–5.13 (m, 2H), 3.56 (td, $J = 6.8$, 6.2 Hz, 2H), 2.98 (dt, $J = 7.1$, 1.0 Hz, 2H), 2.92 ppm (t, $J = 6.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 170.9$ (C), 135.1 (C), 131.3 (CH), 129.3 (C), 125.1 (CH), 123.4 (CH), 121.4 (CH), 120.2 (CH_2), 112.9 (CH), 112.85 (C), 112.80 (C), 41.8 (CH_2), 40.2 (CH_2), 25.2 ppm (CH_2); HRMS-ESI: m/z: calcd: 307.0441 $[M+H]^+$, 309.0421; found: 307.0433, 309.0419 ($\Delta = 2.4$ ppm).

(*S*)-Methyl 2-(but-3-enamido)-3-(1*H*-indol-3-yl)propanoate (9): Compound **9** was prepared by following the general procedure A as described above from **34** (1.62 g, 7.45 mmol). The residue was purified by flash chromatography (50:50 pentane/EtOAc) to give **9** as a waxy solid (1.99 g, 93%). $[\alpha]_D^{20} = +44.6$ ($c = 1.0$ in $CHCl_3$); IR (neat): $\tilde{\nu} = 3293$, 2951, 1734, 1652, 1515, 1434, 1204 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 8.41$ (brs, 1H), 7.55–7.51 (m, 1H), 7.39–7.34 (m, 1H), 7.24–7.07 (m, 2H), 6.96 (d, $J = 2.2$ Hz, 1H), 6.16 (d, $J = 7.9$ Hz, 1H), 5.84 (ddt, $J = 16.8$, 10.5, 7.1 Hz, 1H), 5.18–5.07 (m, 2H), 4.95 (dt, $J = 7.9$, 5.3 Hz, 1H), 3.70 (s, 3H), 3.33 (dt, $J = 5.4$, 0.7 Hz, 2H), 2.98 ppm (dt, $J = 7.1$, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 172.4$ (C), 170.4 (C), 136.2 (C), 130.8 (CH), 127.8 (C), 122.9 (CH), 122.3 (CH), 120.0 (CH_2), 119.7 (CH), 118.7 (CH), 111.4 (CH), 109.9 (C), 53.2 (CH_3), 52.5 (CH), 41.4 (CH_2), 27.6 ppm (CH_2); HRMS-ESI: m/z: calcd: 287.1390 $[M+H]^+$; found: 287.1397 ($\Delta = 2.4$ ppm).

***N*-[5-(Trimethylsilyl)pent-3-enyl]but-3-enamide (10)**: Compound **10** was prepared by following the general procedure A as described above from **36** (500 mg, 3.18 mmol). The residue was purified by flash chromatography (85:15 pentane/EtOAc) to give **10** as a colorless oil (615 mg, 86%). IR (neat): $\tilde{\nu} = 3292$, 3081, 2953, 1648, 1552, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 5.98$–5.84 (m, 1H), 5.67 (brs, 1H), 5.56–5.42 (m, 1H), 5.23–5.12 (m, 3H), 3.28–3.22 (m, 2H), 2.99–2.96 (m, 2H), 2.23–2.14 (m, 2H), 1.48–1.41 (m, 2H), 0.00 (s, 2.7H), −0.01 ppm (s, 5.7H); ^{13}C NMR ($CDCl_3$, 75 MHz): major isomer: $\delta = 170.5$ (C), 131.6 (CH), 129.5 (CH), 124.8 (CH), 119.6 (CH_2), 41.7 (CH_2), 39.4 (CH_2), 32.7 (CH_2), 22.9 (CH_2), −1.9 ppm (CH_3); HRMS-ESI: m/z: calcd: 226.1622 $[M+H]^+$; found: 226.1626 ($\Delta = 2.1$ ppm).

4-Formyl-*N*-[(*R*)-2-methoxy-1-phenylethyl]butanamide (11) (regioisomeric mixture, diagnostic peak only): Compound **11** was prepared by following the general procedure B as described above from **2** (50 mg, 0.023 mmol) in THF. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 9.78$ (t, $J = 1.3$ Hz, 1H), 3.66 (d, $J = 4.9$ Hz, 2H), 3.38 (s, 3H), 2.56–2.51 (m, 2H), 2.34–2.29 (m, 2H), 1.99 ppm (t, $J = 7.1$ Hz, 2H).

3-Formyl-*N*-[(*R*)-2-methoxy-1-phenylethyl]butanamide (12) (diastereomeric mixture, diagnostic peak only): Compound **12** was prepared by following the general procedure B as described above from **2** (50 mg, 0.023 mmol) in THF. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 9.74$ (d, $J = 0.9$ Hz, 0.5H), 9.71 (d, $J = 0.9$ Hz, 0.5H), 1.21 (d, $J = 7.4$ Hz, 1.5H), 1.17 ppm (d, $J = 7.4$ Hz, 1.5H).

***N*-[(1*R*)-2-Methoxy-1-phenylethyl]butanamide (13)**: Compound **13** was prepared by following the general procedure B as described above from **2** (50 mg, 0.023 mmol) in THF. Purification conditions: 50:50 pentane/EtOAc; slightly yellow oil; $[\alpha]_D^{20} = -61.7$ ($c = 0.67$ in $CHCl_3$); IR (neat): $\tilde{\nu} = 3292$, 2961, 2928, 2873, 1640, 1540 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.34$–7.26 (m, 5H), 6.19 (d, $J = 6.6$ Hz, 1H), 5.19 (dt, $J = 7.9$, 4.8 Hz, 1H), 3.66 (d, $J = 4.8$ Hz, 2H), 3.36 (s, 3H), 2.22 (t, $J = 7.5$ Hz, 2H), 1.69 (sext, $J = 7.5$ Hz, 2H), 0.95 ppm (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 172.6$ (C), 140.1 (C), 128.6 (CH), 127.5 (CH), 126.9 (CH), 75.1 (CH_2), 59.2 (CH_3), 52.4 (CH), 38.8 (CH_2), 19.3 (CH_2), 13.9 ppm (CH_3); HRMS-ESI: m/z: calcd: 222.1489 $[M+H]^+$; found: 222.1485 ($\Delta = 1.5$ ppm).

(2*E*)-*N*-[(1*R*)-2-Methoxy-1-phenylethyl]but-2-enamide (14): Compound **14** was prepared by following the general procedure B as described above from **2** (50 mg, 0.023 mmol) in THF. Purification conditions: 50:50

pentane/EtOAc; white solid; $[\alpha]_D^{20}=-74.3$ ($c=1.0$ in $CHCl_3$); m.p. 86–87 °C; IR (neat): $\tilde{\nu}=3275$, 2882, 1669, 1633, 1556 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=7.25$–7.15 (m, 5H), 6.78 (dq, $J=15.1$, 6.9 Hz, 1H), 6.18 (br d, $J=7.6$ Hz, 1H), 5.79 (dq, $J=15.1$, 1.6 Hz, 1H), 5.16 (dt, $J=7.6$, 4.9 Hz, 1H), 3.60 (m, 2H), 3.27 (s, 3H), 1.77 ppm (dd, $J=6.9$, 1.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.5 (C), 140.4 (CH), 140.0 (C), 128.6 (CH), 127.5 (CH), 126.9 (CH), 125.0 (CH), 75.0 (CH_2), 59.1 (CH_3), 52.5 (CH), 17.8 ppm (CH_3); HRMS-ESI: m/z: calcd: 220.1332 $[M+H]^+$; found: 220.1328 ($\Delta=1.7$ ppm).

1-[(1*R*)-2-Methoxy-1-phenylethyl]-3,4-dihydropyridin-2(1*H*)one (15): Compound **15** was prepared by following the general procedure B as described above from **2** (50 mg, 0.023 mmol) in THF. Purification conditions: 50:50 pentane/EtOAc; slightly yellow oil; $[\alpha]_D^{20}=-89.0$ ($c=1.0$ in $CHCl_3$); IR (neat): $\tilde{\nu}=2894$, 1662 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): $\delta=$ 7.37–7.29 (m, 5H), 6.07 (dt, $J=8.0$, 1.5 Hz, 1H), 6.05 (t, $J=6.7$ Hz, 1H), 5.15 (dt, $J=8.0$, 4.2 Hz, 1H), 3.89 (m, 2H), 3.43 (s, 3H), 2.63 (m, 2H), 2.33 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=169.7$ (C), 137.7 (C), 128.7 (CH), 127.7 (CH), 127.6 (CH), 126.6 (CH), 106.3 (CH), 72.1 (CH_2), 59.0 (CH_3), 53.6 (CH), 31.7 (CH_2), 20.0 ppm (CH_2); HRMS-ESI: m/z: calcd: 232.1332 $[M+H]^+$; found: 232.1335 ($\Delta=1.1$ ppm).

1-[(1*R*)-2-Methoxy-1-phenylethyl]-4-methyl-1,5-dihydro-2*H*-pyrrol-2-one (16): Compound **16** was prepared by following the general procedure B as described above from **2** (50 mg, 0.023 mmol) in THF. Purification conditions: 50:50 pentane/EtOAc; slightly yellow oil; $[\alpha]_D^{20}=-60.5$ ($c=1.0$ in $CHCl_3$); IR (neat): $\tilde{\nu}=2922$, 1672 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=$ 7.28–7.18 (m, 5H), 5.78 (m, 1H), 5.44 (dd, $J=6.9$, 5.6 Hz, 1H), 3.89 (d, $J=19.5$ Hz, 1H), 3.88 (dd, $J=10.2$, 2.8 Hz, 1H), 3.75 (dd, $J=10.2$, 5.4 Hz, 1H), 3.57 (d, $J=19.5$ Hz, 1H), 3.32 (s, 3H), 1.93 ppm (d, $J=1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.3 (C), 155.8 (C), 138.1 (C), 128.7 (CH), 127.7 (CH), 127.6 (CH), 122.6 (CH), 72.5 (CH_2), 58.9 (CH_3), 53.2 (CH_2), 53.0 (CH), 15.4 ppm (CH_3); HRMS-ESI: m/z: calcd: 232.1332 $[M+H]^+$; found: 232.1337 ($\Delta=2.2$ ppm).

(3*R*,8a*S*)-3-Phenyltetrahydro-2*H*-oxazolo[3,2-*a*]pyridin-5(3*H*)one (21a): Compound **21a** was prepared by following the general procedure B as described above from **3a** (150 mg, 0.73 mmol) in THF. The residue was purified by flash chromatography (98:2 CH_2Cl_2/MeOH) to give **21a** as pale-yellow solid (135 mg, 85%). $[\alpha]_D^{20}=-87.5$ ($c=0.6$ in CH_2Cl_2) (lit.:[27] $[\alpha]_D^{22}=-88.0$ ($c=0.6$ in CH_2Cl_2); m.p. 87–88 °C (lit.:[28] m.p. 88–90 °C); IR (neat): $\tilde{\nu}=2930$, 2871, 1650, 1443, 1307, 996, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): $\delta=7.40$–7.23 (m, 5H), 5.28 (t, $J=7.9$ Hz, 1H), 5.03 (dd, $J=$ 8.9, 4.6 Hz, 1H), 4.50 (dd, $J=8.9$, 7.8 Hz, 1H), 3.77 (dd, $J=8.9$, 7.8 Hz, 1H), 2.54 (ddm, $J=18.0$, 6.0 Hz, 1H), 2.38 (m, 1H), 2.34 (ddd, $J=18.0$, 11.4, 6.4 Hz, 1H), 1.98 (m, 1H), 1.75 (m, 1H), 1.55 ppm (dddd, $J=13.0$, 12.2, 9.0, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=168.9$ (C), 139.6 (C), 128.8 (CH), 127.5 (CH), 126.1 (CH), 88.7 (CH), 72.4 (CH_2), 58.1 (CH), 31.3 (CH_2), 28.4 (CH_2), 17.1 ppm (CH_2); LRMS-ESI: m/z: 218 $[M+H]^+$, 240 $[M+Na]$; HRMS-ESI: m/z: calcd: 218.1176 $[M+H]^+$; found: 218.1169 ($\Delta=3.0$ ppm).

(3*R*,8a*R*)-3-Phenyltetrahydro-2*H*-oxazolo[3,2-*a*]pyridin-5(3*H*)one (21a′): Purification conditions: 98:2 CH_2Cl_2/MeOH; waxy solid (13 mg, 8%); $[\alpha]_D^{20}=-52.2$ ($c=0.6$ in CH_2Cl_2) (lit.:[3] $[\alpha]_D^{22}=-51.0$ ($c=2.2$ in CH_2Cl_2)); IR (neat): $\tilde{\nu}=2956$, 2872, 1651, 1467 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): $\delta=7.33$–7.22 (m, 5H), 4.92 (dd, $J=6.4$, 1.0 Hz, 1H), 4.84 (dd, $J=9.3$, 3.5 Hz, 1H), 4.15 (dd, $J=9.0$, 6.7 Hz, 1H), 4.01 (dd, $J=9.0$, 1.2 Hz, 1H), 2.43–2.26 (m, 3H), 2.03 (m, 1H), 1.82–1.73 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=167.5$ (C), 141.6 (C), 128.7 (CH), 127.6 (CH), 126.5 (CH), 89.0 (CH), 73.9 (CH_2), 58.9 (CH), 31.2 (CH_2), 28.4 (CH_2),17.9 ppm (CH_2); HRMS-ESI: m/z: calcd: 218.1176 $[M+H]^+$; found: 218.1170 ($\Delta=$ 2.5 ppm).

(3*R*,8a*S*)-3-Benzylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridin-5-one (21b): Compound **21b** was prepared by following the general procedure B as described above from **3b** (200 mg, 0.91 mmol) in THF. The residue was purified by flash chromatography (98:2 EtOAc/MeOH) to give **21b** as a white solid (172 mg, 82%). $[\alpha]_D^{20}=-30.7$ ($c=1.0$ in $CHCl_3$); m.p. 65–66 °C; IR (neat): $\tilde{\nu}=1637$, 1450, 1412, 999, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=7.32$–7.17 (m, 5H), 4.54–4.45 (m, 2H), 4.01 (dd, $J=9.0$, 7.6 Hz, 1H), 3.61 (dd, $J=9.0$, 7.6 Hz, 1H), 3.27 (dd, $J=13.3$, 3.6 Hz, 1H), 2.79 (dd, $J=13.3$, 9.2 Hz, 1H), 2.50 (ddt, $J=18.1$, 6.2, 1.6 Hz, 1H), 2.32 (dd, $J=11.6$, 6.5 Hz, 1H), 2.26–2.16 (m, 1H), 1.89 (ddtd, $J=13.9$, 6.6, 3.8, 2.0 Hz, 1H), 1.62 (tddd, $J=13.8$, 11.5, 6.0, 2.6 Hz, 1H), 1.39 ppm (dddd, $J=13.7$, 12.5, 9.1, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=168.7$ (C), 136.9 (C), 129.6 (CH), 128.6 (CH), 126.7 (CH), 87.3 (CH), 69.3 (CH_2), 55.1 (CH), 37.8 (CH_2), 31.4 (CH_2), 28.2 (CH_2), 17.2 ppm (CH_2); HRMS-ESI: m/z: calcd: 232.1332 $[M+H]^+$; found: 220.1330 ($\Delta=0.8$ ppm).

(3*R*,8a*R*)-3-Benzylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridin-5-one (21b′) (nonisolated, diagnostic peak only): ^1H NMR ($CDCl_3$, 300 MHz): $\delta=4.68$ (dd, $J=9.9$, 3.4 Hz, 2H), 4.24 (ddd, $J=9.4$, 6.5, 3.2 Hz, 2H), 3.78–3.73 ppm (m, 2H).

(3*S*,8a*R*)-3-Isopropylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridin-5-one (21c): Compound **21c** was prepared by following the general procedure B as described above from **3c** (100 mg, 0.58 mmol) in THF. The residue was purified by flash chromatography (98:2 CH_2Cl_2/MeOH) to give **21c** as a yellow oil (76 mg, 71%). $[\alpha]_D^{20}=+3.2$ ($c=1.0$ in $CHCl_3$) (lit.:[34] $[\alpha]_D^{20}=+13$ ($c=1.1$ in EtOH)); IR (neat): $\tilde{\nu}=2957$, 2873, 1648, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=4.73$ (dd, $J=8.6$, 4.7 Hz, 1H), 4.19 (br dt, $J=7.3$, 6.9 Hz, 1H), 4.03 (dd, $J=8.3$, 8.0 Hz, 1H), 3.66 (dd, $J=8.6$, 6.9 Hz, 1H), 2.49 (br ddt, $J=17.9$, 5.8, 1.9 Hz, 1H), 2.34–2.10 (m, 3H), 1.95–1.85 (m, 1H), 1.75–1.60 (m, 1H), 1.49–1.37 (m, 1H), 0.92 (d, $J=$ 6.5 Hz, 3H), 0.89 ppm (d, $J=6.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=169.3$ (C), 87.7 (CH), 66.6 (CH_2), 59.2 (CH), 31.7 (CH_2), 30.1 (CH), 28.5 (CH_2), 19.1 (CH_2), 17.0 ppm (CH_3); HRMS-ESI: m/z: calcd: 184.1332 $[M+H]^+$; found: 184.1328 ($\Delta=2.4$ ppm).

(3*S*,8a*S*)-3-Isopropylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridin-5-one (21c′) (nonisolated, diagnostic peak only): ^1H NMR ($CDCl_3$, 300 MHz): $\delta=4.65$ (dd, $J=9.6$, 3.2 Hz, 1H), 3.97–3.94 (m, 1H), 2.86–2.75 (m, 1H), 0.76 ppm (d, $J=7.0$ Hz, 3H).

(2*S*,3*R*,8a*S*)-3-Methyl-2-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridin-5-one (21d): Compound **21d** was prepared by following the general procedure B as described above from **3d** (150 mg, 0.68 mmol) in THF. The residue was purified by flash chromatography (30:70 to 0:100 pentane/EtOAc) to give **21d** as a colorless oil (123 mg, 78%). $[\alpha]_D^{20}=+77.3$ ($c=$ 1.0 in $CHCl_3$); IR (neat): $\tilde{\nu}=2958$, 1628, 1448, 1329 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=7.38$–7.26 (m, 5H), 5.28 (dd, $J=9.3$, 4.2 Hz, 1H), 5.14 (d, $J=6.1$ Hz, 1H), 4.87 (dq, $J=6.6$, 6.6 Hz, 1H), 2.53–2.44 (m, 1H), 2.41–2.29 (m, 2H), 1.99–1.90 (m, 1H), 1.78–1.63 (m, 1H), 1.61–1.48 (m, 1H), 0.81 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=167.6$ (C), 137.4 (C), 128.4 (CH), 127.8 (CH), 126.1 (CH), 86.0 (CH), 80.0 (CH), 53.4 (CH), 30.9 (CH_2), 29.3 (CH_2), 16.7 (CH_2), 14.1 ppm (CH_3); HRMS-ESI: m/z: calcd: 232.1332 $[M+H]^+$; found: 232.1330 ($\Delta=$ 1.0 ppm).

(2*S*,3*R*,8a*R*)-3-Methyl-2-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridin-5-one (21d′): Colorless oil; yield: 20 mg, 13%; $[\alpha]_D^{20}=+59.2$ ($c=1.0$ in $CHCl_3$); IR (neat): $\tilde{\nu}=2953$, 1635, 1442, 1399, 1328 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): $\delta=7.39$–7.30 (m, 5H), 5.11 (d, $J=6.2$ Hz, 1H), 4.93 (dd, $J=9.4$, 3.2 Hz, 1H), 4.33 (dq, $J=6.3$, 6.2 Hz, 1H), 2.44–2.33 (m, 3H), 2.10–1.96 (m, 1H), 1.85–1.60 (m, 2H), 0.88 ppm (d, $J=6.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=168.2$ (C), 135.7 (C), 128.4 (CH), 128.0 (CH), 126.2 (CH), 88.2 (CH), 81.5 (CH), 55.0 (CH), 31.1 (CH_2), 28.9 (CH_2), 17.5 (CH_2), 14.5 ppm (CH_3); HRMS-ESI m/z: calcd: 232.1332 $[M+H]^+$; found: 232.1335 ($\Delta=1.2$ ppm).

1,2,3,6,7-Hexahydro-9-methoxy-4*H*-benzo[*a*]quinolizin-4-one (22): Compound **22** was prepared by following the general procedure B as described above from **4** (100 mg, 0.46 mmol) in THF. The residue was purified by flash chromatography (20:80 to 0:100 pentane/EtOAc) to give **22** as a yellow oil (94 mg, 90%). IR (neat): $\tilde{\nu}=2929$, 2837, 1606, 1503, 1464, 1237 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=7.12$ (d, $J=8.4$ Hz, 1H), 6.79 (dd, $J=8.4$, 2.7 Hz, 1H), 6.67 (d, $J=2.7$ Hz, 1H), 4.81–4.75 (m, 1H), 4.61 (dd, $J=10.3$, 4.6 Hz, 1H), 3.79 (s, 3H), 2.97–2.87 (m, 2H), 2.75–2.68 (m, 1H), 2.59–2.48 (m, 2H), 2.36 (ddd, $J=17.6$, 11.4, 6.4 Hz, 1H), 1.99–1.80 (m, 2H), 1.74–1.61 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=169.5$ (C), 158.2 (C), 136.5 (C), 129.7 (C), 126.1 (CH), 113.5 (CH), 112.8 (CH), 56.6 (CH), 55.4 (CH_3), 39.8 (CH_2), 32.3 (CH_2), 30.7 (CH_2), 29.3 (CH_2), 19.7 ppm (CH_2); HRMS-ESI: m/z: calcd: 232.1332 $[M+H]^+$; found: 232.1328 ($\Delta=1.7$ ppm).

1,2,3,6,7-Hexahydro-9,10-dimethoxy-4*H*-benzo[*a*]quinolizin-4-one (23):[35] Compound **23** was prepared by following the general procedure B as de-

scribed above from **5** (100 mg, 0.40 mmol) in THF. The residue was purified by flash chromatography (98:2 EtOAc/MeOH) to give **23** as a yellow oil (92 mg, 88%). IR (neat): $\tilde{\nu}$ = 2935, 2835, 1609, 1511, 1463, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.68 (s, 1H), 6.63 (s, 1H), 4.91–4.85 (m, 1H), 4.62 (dd, J = 10.6, 4.4 Hz, 1H), 3.87 (s, 6H), 2.33–2.90 (m, 6H), 1.65–2.00 ppm (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 169.5 (C), 147.9 (C), 147.8 (C), 129.2 (C), 127.4 (C), 111.6 (CH), 108.3 (CH), 56.8 (CH), 56.2 (CH_3), 56.0 (CH_3), 39.8 (CH_2), 32.3 (CH_2), 31.0 (CH_2), 28.6 (CH_2), 19.7 ppm (CH_2); HRMS-ESI: m/z: calcd: 262.1438 $[M+H]^+$; found: 262.1431 (Δ = 2.5 ppm).

(6*S*,11b*R*)-Methyl 2,3,4,6,7,11b-hexahydro-9,10-dimethoxy-4-oxo-1*H*-pyrido[2,1-*a*]isoquinoline-6-carboxylate (24): Compound **24** was prepared by following the general procedure B as described above from **6** (150 mg, 0.49 mmol) in THF. The residue was purified by flash chromatography (EtOAc) to give **24** (131 mg, 84%) as a white solid. $[\alpha]_D^{20}$ = +123.2 (c = 1.0 in $CHCl_3$); m.p. 149–150 °C; IR (neat): $\tilde{\nu}$ = 2931, 2855, 1735, 1640, 1621, 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.62 (br s, 2H), 5.75 (dd, J = 5.9, 3.5 Hz, 1H), 4.79 (dd, J = 11.0, 4.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.65 (s, 3H), 3.17 (dd, J = 15.8, 3.5 Hz, 1H), 3.06 (dd, J = 15.8, 6.6 Hz, 1H), 2.66 (dtd, J = 17.7, 4.7, 1.3 Hz, 1H), 2.51–2.40 (m, 2H), 2.05–1.94 (m, 2H), 1.75–1.64 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 171.5 (C), 170.5 (C), 148.2 (C), 148.1 (C), 128.0 (C), 124.2 (C), 111.4 (CH), 108.4 (CH), 56.1 (CH_3), 56.0 (CH_3), 54.8 (CH), 52.4 (CH_3), 50.5 (CH), 31.9 (CH_2), 31.6 (CH_2), 30.2 (CH_2), 19.6 ppm (CH_2); HRMS-ESI: m/z: calcd: 320.1492 $[M+H]^+$; found: 320.1483 (Δ = 2.8 ppm).

1,2,3,6,7,12b-Hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)one (25): Compound **25** was prepared by following the general procedure B as described above from **7** (200 mg, 0.88 mmol) in THF. The residue was purified by flash chromatography (99:1 EtOAc/MeOH) to give **25** (180 mg, 85%) as a white solid. M.p. 240–241 °C; IR (neat): $\tilde{\nu}$ = 3200, 2921, 2851, 1607, 1437 cm^{-1}; ^1H NMR ($CDCl_3$+CD_3OD, 300 MHz): δ = 7.49 (br d, J = 7.5 Hz, 1H), 7.33 (br d, J = 7.9 Hz, 1H), 7.16 (td, J = 7.5, 1.4 Hz, 1H), 7.10 (td, J = 7.5, 1.5 Hz, 1H), 5.17–5.07 (m, 1H), 4.78 (br dd, J = 9.8, 4.8 Hz, 1H), 2.89–2.74 (m, 3H), 2.63–2.55 (m, 1H), 2.50–2.34 (m, 2H), 1.98–1.91 (m, 1H), 1.87–1.72 ppm (m, 2H); ^{13}C NMR ($CDCl_3$+CD_3OD, 50 MHz): δ = 170.2 (C), 136.4 (C), 133.4 (C), 126.6 (C), 121.8 (CH), 119.4 (CH), 118.2 (CH), 111.1 (CH), 108.6 (C), 54.7 (CH), 40.5 (CH_2), 32.2 (CH_2), 28.7 (CH_2), 21.0 (CH_2), 19.2 ppm (CH_2); HRMS-ESI: m/z: calcd: 241.1335 $[M+H]^+$; found: 241.1342 (Δ = 2.6 ppm).

9-Bromo-1,2,3,6,7,12b-hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)one (26): Compound **26** was prepared by following the general procedure B as described above from **8** (100 mg, 0.33 mmol) in THF. The residue was purified by flash chromatography (EtOAc purum) to give **26** (76 mg, 73%) as a white solid. M.p. 272–274 °C; IR (neat): $\tilde{\nu}$ = 3165, 2934, 1609, 1437, 1311 cm^{-1}; ^1H NMR ($CDCl_3$+CD_3OD, 300 MHz): δ = 7.59 (d, J = 1.6 Hz, 1H), 7.24–7.17 (m, 2H), 5.15–5.05 (m, 1H), 4.75 (br dd, J = 9.6, 4.5 Hz, 1H), 2.87–2.67 (m, 3H), 2.63–2.54 (m, 1H), 2.50–2.32 (m, 2H), 1.96–1.71 ppm (m, 3H); ^{13}C NMR ($CDCl_3$+CD_3OD, 75 MHz): δ = 170.2 (C), 135.1 (C), 134.8 (C), 128.3 (C), 124.4 (CH), 120.7 (CH), 112.5 (CH), 112.4 (C), 108.2 (C), 54.6 (CH), 40.4 (CH_2), 32.2 (CH_2), 28.5 (CH_2), 20.8 (CH_2), 19.1 ppm (CH_2); HRMS-ESI: m/z: calcd: 319.0441 $[M+H]^+$, 321.0421; found: 319.0446, 321.0429 (Δ = 1.7 ppm).

(6*S*,12b*R*)-Methyl 1,2,3,4,6,7,12,12b-octahydro-4-oxoindolo[2,3-*a*]quinolizine-6-carboxylate (27): Compound **27** was prepared by following the general procedure B as described above from **9** (150 mg, 0.52 mmol) in THF. The residue was purified by flash chromatography (25:75 pentane/EtOAc) to give **27** (139 mg, 89%) as a pale-yellow solid. M.p. 165–167 °C; IR (neat): $\tilde{\nu}$ = 3273, 2952, 2850, 1737, 1610, 1429 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.07 (br s, 1H), 7.53 (dd, J = 6.6, 2.0 Hz, 1H), 7.35–7.30 (m, 1H), 7.24–7.09 (m, 2H), 6.12 (dd, J = 6.4, 1.4 Hz, 1H), 5.11–5.03 (m, 1H), 3.63 (s, 3H), 3.46 (dt, J = 15.7, 1.6 Hz, 1H), 3.07 (ddd, J = 15.7, 6.4, 2.4 Hz, 1H), 2.78–2.64 (m, 1H), 2.54–2.40 (m, 2H), 2.07–1.97 (m, 2H), 1.83–1.75 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 171.6 (C), 170.5 (C), 136.6 (C), 132.5 (C), 126.8 (C), 122.4 (CH), 119.9 (CH), 118.5 (CH), 111.1 (CH), 106.6 (C), 52.6 (CH_3), 52.2 (CH), 50.1 (CH), 32.2 (CH_2), 29.8 (CH_2), 22.9 (CH_2), 19.7 ppm (CH_2); $[\alpha]_D^{20}$ = +129.2 (c = 1 in $CHCl_3$); HRMS-ESI: m/z: calcd: 299.1390 $[M+H]^+$; found: 299.1385 (Δ = 1.9 ppm).

(6*S*,12b*S*)-Methyl 1,2,3,4,6,7,12,12b-octahydro-4-oxoindolo[2,3-*a*]quinolizine-6-carboxylate (27′): The residue was purified by flash chromatography (25:75 to 0:100 pentane/EtOAc) to give **27′** as a yellow solid. $[\alpha]_D^{20}$ = −40.2 (c = 1 in $CHCl_3$); m.p. 197 °C; IR (neat): $\tilde{\nu}$ = 3269, 2919, 2852, 1742, 1615, 1467 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ = 8.51 (br s, 1H), 7.54–7.50 (m, 1H), 7.37–7.31 (m, 1H), 7.23–7.12 (m, 2H), 4.98–4.92 (m, 1H), 4.43 (dd, J = 8.4, 4.9 Hz, 1H), 3.72 (s, 3H), 3.45 (ddd, J = 15.7, 8.4, 1.9 Hz, 1H), 3.05 (ddd, J = 15.7, 4.9, 1.9 Hz, 1H), 2.53–2.35 (m, 3H), 2.23–2.15 (m, 1H), 2.00–1.74 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 172.2 (C), 170.8 (C), 136.4 (C), 133.2 (C), 126.9 (C), 122.4 (CH), 120.0 (CH), 118.4 (CH), 111.3 (CH), 108.9 (C), 56.8 (CH), 54.9 (CH), 52.4 (CH_3), 32.5 (CH_2), 27.2 (CH_2), 22.7 (CH_2), 18.4 ppm (CH_2); HRMS-ESI: m/z: calcd: 299.1390 $[M+H]^+$; found: 299.1392 (Δ = 0.5 ppm).

5-Bromopent-2-enyl)trimethylsilane (28): Grubbs II catalyst (44 mg, 0.052 mmol) was added to a solution of 1-bromo-3-butene (700 mg, 5.19 mmol) and allyltrimethylsilane (3.30 mL, 20.74 mmol). The suspension was heated under microwaves for 1 min at 60 °C. After cooling, the excess of the reactive compounds were evaporated under reduced pressure and the residue was purified by flash chromatography (heptane purum) to give **28** as a colorless oil (769 mg, E/Z 63:37, 67%). IR (neat): $\tilde{\nu}$ = 2954, 1246, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.61–5.48 (m, 1H), 5.31–5.17 (m, 1H), 3.36–3.35 (m, 2H), 2.59–2.51 (m, 2H), 1.51–1.43 (m, 2H), 0.02 (s, 3.3H), 0.01 ppm (s, 5.7H); ^{13}C NMR ($CDCl_3$, 50 MHz): minor Z isomer: δ = 128.9 (CH), 123.6 (CH), 32.6 (CH_2), 30.9 (CH_2), 19.0 (CH_2), −1.7 ppm (CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): major E isomer: δ = 130.2 (CH), 124.9 (CH), 36.4 (CH_2), 33.4 (CH_2), 23.0 (CH_2), −1.9 ppm (CH_3); GCMS m/z: 222 $[M]^+$, 139, 73.

3,4-Dihydro-1-[5-(trimethylsilyl)pent-3-enyl]pyridine-2(1*H*)one (29): Compound **29** was prepared by following the general procedure B as described above from **10** (100 mg, 0.44 mmol) in THF. The residue was purified by flash chromatography (85:15 pentane/EtOAc) to give **29** a colorless oil (82 mg, 78%). IR (neat): $\tilde{\nu}$ = 2951, 1668, 1406, 1384, 1246, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ = 6.02–5.96 (m, 1H), 5.52–5.36 (m, 1H), 5.24–5.04 (m, 2H), 3.43 (br t, J = 7.3 Hz, 2H), 2.52–2.43 (m, 2H), 2.32–2.20 (m, 4H), 1.46 (dd, J = 8.5, 1.0 Hz, 0.6H), 1.39 (dd, J = 7.8, 1.0 Hz, 1.4H), −0.01 (s, 2.3H), −0.04 ppm (s, 5.6H); ^{13}C NMR ($CDCl_3$, 75 MHz): major E isomer: δ = 169.2 (C), 130.2 (CH), 129.2 (CH), 124.6 (CH), 105.7 (CH), 46.6 (CH_2), 32.2 (CH_2), 31.6 (CH_2), 22.9 (CH_2), 20.4 (CH_2), −1.9 ppm (CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): minor Z isomer: δ = 169.3 (C), 130.1 (CH), 128.3 (CH), 123.0 (CH), 105.8 (CH), 46.2 (CH_2), 33.7 (CH_2), 31.6 (CH_2), 26.5 (CH_2), 18.7 (CH_2), −1.7 ppm (CH_3); HRMS-ESI: m/z: calcd: 238.1622 $[M+H]^+$; found: 238.1629 (Δ = 3.2 ppm).

Hexahydro-1-vinylindolizin-5(1*H*)one (30):[33b] In a stainless steel autoclave under an inert atmosphere, a solution of dicarbonylacetylacetonato rhodium (1.7 mg, 0.007 mmol) and biphephos (10.5 mg, 0.013 mmol) in anhydrous degassed CH_2Cl_2 (3 mL), prepared in a Schlenk glassware under an inert atmosphere, was added to a solution of **10** (150 mg, 0.665 mmol) in anhydrous degassed CH_2Cl_2 to reach a final concentration of 0.04 M. The autoclave was flushed with H_2/CO 1:1 three times. Then, the autoclave was filled with 5 atm of H_2/CO 1:1 and was heated at 60 °C with stirring for 4 h. Then, the autoclave was cooled to room temperature and the gases were slowly and carefully released. TFA (49 μL, 0.665 mmol) was added and the solution was stirred at room temperature for 12 h. The reaction mixture was then concentrated under reduced pressure to give an oil. The residue was purified by flash chromatography (98:2 CH_2Cl_2/MeOH) to give **30** as a pale-yellow oil (90 mg, 82%) as a mixture of isomers (*cis*/*trans* 90:10). IR (neat): $\tilde{\nu}$ = 2946, 2878, 1613, 1467, 1412, 1331 cm^{-1}

*Major isomer (*cis ***30***)*: ^1H NMR ($CDCl_3$, 200 MHz): δ = 5.60 (ddd, J = 17.8, 9.5, 9.5 Hz, 1H), 5.08 (dd, J = 11.5, 1.5 Hz, 2H), 3.72–3.41 (m, 3H), 2.79 (dt, J = 9.3, 5.5 Hz, 1H), 2.48–2.23 (m, 2H), 2.03–1.61 (m, 5H), 1.40–1.25 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.8 (C), 135.8 (CH), 116.7 (CH_2), 61.8 (CH), 46.6 (CH), 43.5 (CH_2), 31.0 (CH_2), 28.6 (CH_2), 25.5 (CH_2), 20.9 ppm (CH_2).

*Minor isomer (*trans ***30′****, diagnostic peak only)*: ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.06 (td, J = 10.5, 3.2 Hz, 1H); HRMS-ESI: m/z: calcd: 166.1226 $[M+H]^+$; found: 166.1228 (Δ = 0.8 ppm).

3-(Octahydro-5-oxoindolizin-1-yl)propanal (31): Compound **31** was prepared by following the general procedure B as described above from **10** (100 mg, 0.44 mmol) in THF. The residue was purified by flash chromatography (96:4 CH_2Cl_2/MeOH) to give **31** as a colorless oil (60 mg, 69%) and as a mixture of isomers (*cis*/*trans* 90:10). IR (neat): $\tilde{\nu}$ = 2944, 2873, 1716, 1601, 1470, 1412 cm^{-1}

*Major isomer (*cis ***31***)*: ^1H NMR ($CDCl_3$, 300 MHz): δ = 9.78 (br t, J = 1.0 Hz, 1H), 3.61–3.39 (m, 3H), 2.57–2.37 (m, 3H), 2.30–2.09 (m, 3H), 2.00–1.66 (m, 5H), 1.47–1.21 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 201.6 (CH), 169.5 (C), 61.9 (CH), 43.0 (CH_2), 41.9 (CH_2), 40.7 (CH), 31.1 (CH_2), 26.5 (CH_2), 24.9 (CH_2), 21.1 (CH_2), 19.5 ppm (CH_2).

*Minor isomer (*trans ***31′***, diagnostic peak only)*: ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.99 (td, J = 10.4, 4.0 Hz, 1H); HRMS-ESI: m/z: calcd: 196.1332 $[M+H]^+$; found: 196.1327 (Δ = 2.6 ppm).

(1*R*)-2-Methoxy-1-phenylethanamine (32): (*R*)-(−)-2-Amino-2-phenylethanol (2.00 g, 14.58 mmol) in THF (20 mL) was added dropwise to a suspension of sodium hydride 60% in mineral oil (1.224 g, 30.62 mmol) in THF (10 mL), and the suspension was stirred for 2 h at room temperature. Iodomethane (0.95 mL, 15.31 mmol) was added and the solution was stirred for 1 h, then heated to reflux for a further 3 h. The reaction mixture was cooled, diluted with cold brine, extracted with diethyl ether, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (95:5 CH_2Cl_2/MeOH) to give **32** as a colorless oil (1.894 g, 86%). $[\alpha]_D^{20}$ = −47.4 (c = 0.67 in $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2885, 1452, 1111, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.33–7.18 (m, 5H), 4.12 (dd, J = 8.8, 3.8 Hz, 1H), 3.44 (dd, J = 9.2, 3.8 Hz, 1H), 3.31 (s, 3H), 3.29 (dd, J = 9.3, 8.8 Hz, 1H), 1.71 ppm (br s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 142.5 (C), 128.4 (CH), 127.4 (CH), 126.8 (CH), 79.0 (CH_2), 58.9 (CH_3), 55.4 ppm (CH); LRMS-ESI: m/z: 152 $[M+1]$, 135 $[M-16]$.

(*S*)-Methyl 2-amino-3-(3,4-dimethoxyphenyl)propanoate (33): Acetyl chloride (0.66 mL, 9.32 mmol) was added dropwise to MeOH (5 mL) at 0°C under an argon atmosphere. After 5 min, 3-(3,4-dimethoxyphenyl)-L-alanine (700 mg, 3.11 mmol) was added and the solution was stirred at reflux for 2 h. After cooling, the solvent was evaporated and the residue was dissolved in water. Saturated aqueous $NaHCO_3$ solution was added (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give **33** as a yellow solid (687 mg, 92%), which was used without further purification. $[\alpha]_D^{20}$ = +4.5 (c = 1.0 in $CHCl_3$); m.p. 55–56°C; IR (neat): $\tilde{\nu}$ = 3375, 2962, 2936, 2835, 1729, 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 6.78 (d, J = 8.1 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.69 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.70 (s, 3H), 3.69 (m, 1H), 3.01 (dd, J = 13.6, 5.2 Hz, 1H), 2.80 (dd, J = 13.6, 7.7 Hz, 1H), 1.54 ppm (br s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.5 (C), 149.0 (C), 148.0 (C), 129.6 (C), 121.4 (CH), 112.4 (CH), 111.3 (CH), 55.90 (2CH_3), 55.86 (CH), 52.0 (CH_3), 40.6 ppm (CH_2); LRMS-ESI: m/z: 240.1 $[M+H]^+$, 223.0 $[M-NH_2]^+$.

(*S*)-Methyl 2-amino-3-(1*H*-indol-3-yl)propanoate (34): Acetyl chloride (2.09 mL, 29.4 mmol) was added dropwise to MeOH (13 mL) at 0°C under an argon atmosphere. After 5 min, L-tryptophane (2.00 g, 9.8 mmol) was added and the solution was stirred at reflux for 2 h. After cooling, the solvent was evaporated and the residue was dissolved in water. Saturated aqueous $NaHCO_3$ solution was added (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give **34** as a pale-yellow solid (1.68 g, 79%), which was used without further purification. $[\alpha]_D^{20}$ = +16.9 (c = 1.0 in $CHCl_3$); m.p. 91–92°C; IR (neat): $\tilde{\nu}$ = 3259, 3295, 1727, 1567, 1450, 1224 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.23 (br s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.23–7.11 (m, 2H), 7.06 (d, J = 1.5 Hz, 1H), 3.85 (m, 1H), 3.73 (s, 3H), 3.30 (dd, J = 14.2, 4.7 Hz, 1H), 3.07 (dd, J = 14.2, 7.9 Hz, 1H), 1.63 ppm (br s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.8 (C), 136.4 (C), 127.5 (C), 123.1 (CH), 122.2 (CH), 119.6 (CH), 118.8 (CH), 111.3 (CH), 111.1 (C), 55.1 (CH), 52.1 (CH_3), 30.8 ppm (CH_2); LRMS-ESI: m/z: 219.0 $[M+H]^+$, 202.0 $[M-NH_2]^+$.

5-Azidopent-2-enyltrimethylsilane (35): Sodium azide (1.538 g, 23.67 mmol) was added to a solution of **28** (1.745 g, 7.89 mmol) in DMF (8 mL). The suspension was stirred overnight at 70°C. After cooling, Et_2O (50 mL) was added and the organic layer was washed by H_2O (3×30 mL), dried over Na_2SO_4, filtered, and evaporated to give **35** as a slightly yellow oil (1.325 g, E/Z 63:37, 92%), which was used without further purifications. IR (neat): $\tilde{\nu}$ = 2954, 2089, 1247, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ = 5.64–5.46 (m, 1H), 5.33–5.14 (m, 1H), 3.31–3.21 (m, 2H), 2.36–2.24 (m, 2H), 1.54–1.43 (m, 2H), 0.02 (s, 3.3H), 0.00 ppm (s, 5.7H); ^{13}C NMR ($CDCl_3$, 50 MHz): minor Z isomer: δ = 128.9 (CH), 122.3 (CH), 51.2 (CH_2), 26.9 (CH_2), 18.8 (CH_2), −1.8 ppm (CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) major E isomer: δ = 129.9 (CH), 123.8 (CH), 51.5 (CH_2), 32.4 (CH_2), 22.9 (CH_2), −2.0 ppm (CH_3); GCMS: m/z: 183 $[M]^+$, 101, 86, 73.

5-(Trimethylsilyl)pent-3-en-1-amine (36): Lithium aluminum hydride (0.311 g, 8.20 mmol) was added portionwise to a solution of **35** (1.253 g, 6.83 mmol) in Et_2O (30 mL) at 0°C. The suspension was stirred overnight at room temperature. After this time, in an ice bath, H_2O (0.31 mL) then NaOH 15% (0.31 mL) and H_2O (0.93 mL) were added and the suspension was stirred for 2 h. The suspension was filtered off, and the organic layer was dried over Na_2SO_4, filtered, and evaporated to give **36** as a slightly yellow oil (1.05 g, E/Z 63:37, 98%), which was used without further purifications. IR (neat): $\tilde{\nu}$ = 2952, 1246, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ = 5.59–5.38 (m, 1H), 5.31–5.11 (m, 1H), 2.75–2.65 (m, 2H), 2.20–2.06 (m, 2H), 1.52–1.40 (m, 2H), 1.34 (br s, 2H), 0.01 (s, 3.3H), −0.01 ppm (s, 5.7H); ^{13}C NMR ($CDCl_3$, 50 MHz): minor Z isomer: δ = 127.8 (CH), 124.3 (CH), 31.2 (CH_2), 29.7 (CH_2), 18.7 (CH_2), −1.8 ppm (CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): major E isomer: δ = 128.8 (CH), 125.7 (CH), 42.0 (CH_2), 36.9 (CH_2), 22.9 (CH_2), −1.9 ppm (CH_3); HRMS-ESI: m/z: calcd: 158.1360 $[M+H]^+$; found: 158.1361 (Δ = 0.8 ppm).

Acknowledgements

This work was supported by the Ministère délégué à l'Enseignement Supérieur et à la Recherche (EA, TS). The authors thank P. Wehrung and P. Buisine (IFR85) for HRMS analyses.

[1] L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163.
[2] a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; b) L. F. Tietze, G. Brasche, K. M. Gericke in *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.
[3] T.-L. Ho in *Tandem Organic reactions*, Wiley, NY, **1992**.
[4] P. J. Parsons, A. J. Shell, *Chem. Rev.* **1996**, *96*, 195–206.
[5] D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581.
[6] A. Padwa, K. S. Bur, *Tetrahedron* **2007**, *63*, 5341–5378.
[7] L. E. Overman, L. D. Pennington, *J. Org. Chem.* **2003**, *68*, 7143–7157.
[8] R. W. Hoffmann, D. Brückner, *New J. Chem.* **2001**, *25*, 369–373.
[9] B. Breit, W. Seiche, *Synthesis* **2001**, 1–36.
[10] I. Ojima, C.-Y. Tsai, M. Tzamarioudaki, D. Bonnafoux, "The Hydroformylation Reaction" in *Organic Reactions*, *Vol. 56*, Wiley, New York, **2000**, p. 1 .
[11] W.-H. Chiou, S.-Y. Lee, I. Ojima, *Can. J. Chem.* **2005**, *83*, 681–692.
[12] P. W. N. M. van Leeuwen in *Rhodium-Catalyzed Hydroformylation*, Kluwer, Dordrecht, **2000**.
[13] a) P. Eilbracht, L. Bärfacker, C. Buss, C. Hollmann, B. E. Kitsos-Rzychon, C. L. Kranemann, T. Rische, R. Roggenbuck, A. Schmidt, *Chem. Rev.* **1999**, *99*, 3329–3365; b) P. Eilbracht, A. M. Schmidt, *Top. Organomet. Chem.* **2006**, *18*, 65–95.
[14] a) W.-H. Chiou, N. Mizutani, I. Ojima, *J. Org. Chem.* **2007**, *72*, 1871–1882; b) I. Ojima, M. Tzamarioudaki, M. Eguchi, *J. Org. Chem.* **1995**, *60*, 7078–7079; c) A. Padwa, S. C. Bur, *Tetrahedron* **2007**, *63*, 5341–5378.
[15] R. W. Hoffmann, D. Brückner, V. J. Gerusz, *Heterocycles* **2000**, *52*, 121–124.

[16] D. J. Bergmann, E. M. Campi, W. R. Jackson, A. F. Patti, *Chem. Commun.* **1999**, 1279–1280.
[17] E. Teoh, E. M. Campi, W. R. Jackson, A. J. Robinson, *Chem. Commun.* **2002**, 978–979.
[18] W.-H. Chiou, A. Schoenfelder, L. Sun, A. Mann, I. Ojima, *J. Org. Chem.* **2007**, *72*, 9418–9425.
[19] E. Petricci, A. Mann, A. Schoenfelder, A. Rota, M. Taddei, *Org. Lett.* **2006**, *8*, 3725–3728.
[20] M. D. Mihovilovic, P. Stanetty, *Angew. Chem.* **2007**, *119*, 3684–3688; *Angew. Chem. Int. Ed.* **2007**, *46*, 3612–3615.
[21] N. W. Speckamp, J. M. Molenaar, *Tetrahedron* **2000**, *56*, 3817–3856.
[22] B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. Turchi, C. A. Maryanoff, *Chem. Rev.* **2004**, *104*, 1431–1628.
[23] B. Breit, W. Seiche, *J. Am. Chem. Soc.* **2003**, *125*, 6608–6609.
[24] D. G. Cuny, S. L. Buchwald, *J. Am. Chem. Soc.* **1993**, *115*, 2066–2068.
[25] E. Billig, A. G. Abatjoglou, D. R. Bryant, US 4668651, **1988**.
[26] Stability of biphephos was observed by ^{31}P NMR spectroscopy after heating in solvent for 12 h in presence of acid additives. See the Supporting Information for details.
[27] J. Royer, H.-P. Husson, *Heterocycles* **1993**, *36*, 1493–1496.
[28] M. Amat, J. Bosch, J. Hidalgo, M. Canto, M. Perez, N. Llor, E. Molins, C. Miravitlles, M. Orozco, J. Luque, *J. Org. Chem.* **2000**, *65*, 3074–3084.
[29] For a Pictet–Spengler reaction driven by hydroformylation on solid support, see: G. Dessole, M. Marchetti, M. Taddei, *J. Comb. Chem.* **2003**, *5*, 198–200.
[30] CCDC-696805 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif
[31] a) At present, we have no explanation for that result. Similar observations have been made, see S. M. Allin, S. L. James, M. R. J. Elsegood, W. P. Martin, *J. Org. Chem.* **2002**, *67*, 9464–9467; b) S.-H. Yamada, K. Murato, T. Shioiri, *Tetrahedron Lett.* **1976**, 1605–1608.
[32] A. Michaut, T. Boddaert, Y. Coquerel, J. Rodriguez, *Synthesis* **2007**, 2867–2871.
[33] a) S. M. Amorde, A. S. Judd, S. F. Martin, *Org. Lett.* **2005**, *7*, 2031–2033; b) W. R. Judd, S. Ban, J. Aubé, *J. Am. Chem. Soc.* **2006**, *128*, 13736–13741.
[34] L. Micouin, J.-C. Quirion, H.-P. Husson, *Synth. Commun.* **1996**, *26*, 1605–1611.
[35] Z. Zhang, D. C. Leitch, M. Lu, B. O. Patrick, L. L. Schafer, *Chem. Eur. J.* **2007**, *13*, 2012–2022.

Received: September 1, 2008
Published online: November 13, 2008

