DOI: 10.1002/adsc.201300666

Scope and Post-Transformations for the Borane-Isocyanide Multicomponent Reactions: Concise Access to Structurally Diverse Heterocyclic Compounds

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Received: July 26, 2013; Revised: August 28, 2013; Published online: November 11, 2013

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300666.

Abstract: A recently described family of multicomponent reactions (MCRs) involving isocyanides, aldehydes, dipolarophiles and alkylboranes that yield highly substituted aziridines, oxazolidines and pyrrolidines has been studied in detail. In this work the scope of these processes is significantly increased by preparing the borane input through hydroboration of alkenes or organometallic processes, in tandem with the MCR. The aldehyde range is also expanded, and indole-3-carbaldehydes yield reactive imines and bis-indolyloxazolidines, depending on the electron density of the heterocycle. Finally, the obtained adducts constitute an ideal platform to generate structurally diverse compounds using simple post-condensation modifications. In this way, indole imines undergo stereoselective hydrocyanation and oxazolidines are reductively opened to give amino alcohols. Additionally, palladium-, ruthenium- and gold-catalyzed processes lead to a variety of complex heterocycles. The methodology is simple, efficient and highly divergent, leading to an array of interesting scaffolds for medicinal chemistry.

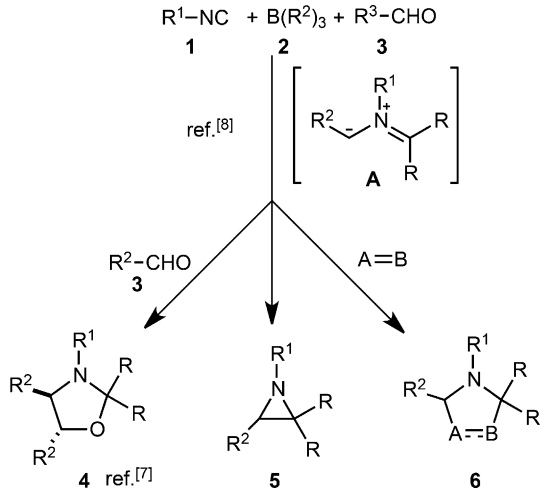
Keywords: boranes; heterocycles; isocyanides; molecular diversity; multicomponent reactions

Introduction

Multicomponent reactions (MCRs) are highly convergent processes in which three or more components react to give a product containing the essential part of the starting materials, in atom- and step-economical protocols.[1] The classic isocyanide-based Ugi and Passerini reactions are ranked among the most productive and useful synthetic processes.[2] Furthermore, MCRs involving heterocyclic compounds constitute one prolific approach to prepare complex molecules and generate chemical diversity in a quick manner, a critical issue in biological and medicinal chemistry research.[3] In this context, remarkable contributions by Orru and Martin focus on the design of new MCRs as flexible strategies towards complexity and diversity.[4] Whenever a multicomponent process tolerates the presence of functional groups not participating in the reaction mechanism, an easy post-transformation can be exploited as the first synthetic step towards highly diverse complex structures. Relevant examples have been described in isocyanide MCRs, leading to complex heterocycles basically in two-step sequences.[5]

Following our interest in the development of new MCRs, we studied the interaction of boranes with isocyanides, as few processes involve boron species in the MCR field.[6] Remarkably, Hesse described in the 1960s, the reaction of isocyanides, aldehydes and boranes to yield oxazolidines **4** (Scheme 1).[7] Recently, we redesigned this process into a new family of MCRs by inclusion of dipolarophiles, allowing in this way access to aziridines **5** and pyrrolidines **6**.[8] The process proceeds through an azomethine ylide intermediate **A**, from the interaction of the isocyanide, borane and aldehyde inputs. The ylide can cyclize to generate aziridines **5**; alternatively it may participate in formal [3+2]cycloadditions with a second equivalent of aldehyde (leading to oxazolidines **4**), or with distinct dipolarophiles, yielding the pyrrolidine scaffold **6** (Scheme 1).

The scope of all components was explored. The aldehyde range included aromatic, heteroaromatic and α,β-unsaturated derivatives. Aromatic aldehydes with



Scheme 1. Multicomponent reactions of isocyanides, boranes, aldehydes and dipolarophiles.

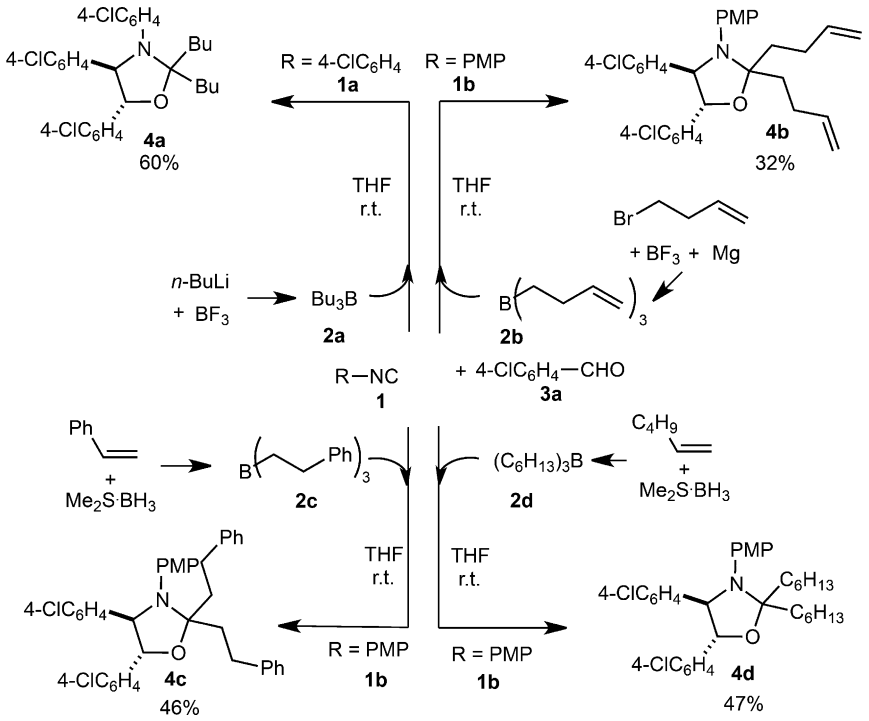
electron-donating groups afforded aziridines. Although the aliphatic isocyanides were not reactive, both electron-rich and electron-poor aromatic isocyanides yielded the expected products. Several dipolarophiles, including *N*-phenylmaleimide, and activated (electron-deficient) alkenes and alkynes, afforded the corresponding pyrrolidines. The borane input resulted to be the main limitation of the reaction, mainly due to the lack of commercially available trialkylboranes. Thus the scope was restricted, in practice, to $B(Et)_3$ and $B(Bu)_3$.

Having in our hands a robust methodology to prepare substituted aziridines, pyrrolidines and oxazolidines, here we report our studies on expanding the scope of this MCR and on the exploitation of the synthetic potential of the obtained products.

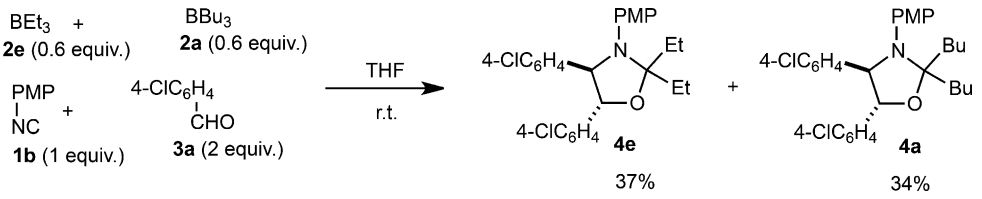
Results and Discussion

In order to overcome the scarcity of trialkylboranes, we took an alternative approach in which these reactants are prepared by reaction of organometals with BF_3, or by hydroboration of alkenes and used *in situ*. First, $B(Bu)_3$ was prepared by reaction of *n*-BuLi with BF_3,[9] and immediately reacted with isocyanide **1a** and aldehyde **3a** to afford oxazolidine **4a** (Scheme 2). In this way, the yield raised to 60% – 20% higher than with commercially available $B(Bu)_3$.[8]

Similarly, trihomoallylborane **2b** was prepared using a modification of the Lyle procedure[10] and oxazolidine **4b** (32%) was thus obtained by addition of *p*-methoxyphenyl-(PMP) isocyanide **1b** and aldehyde **3a** following the general protocol (Scheme 2). Using an analogous strategy, boranes **2c** and **2d** were prepared by hydroboration of the corresponding alkenes with borane-dimethyl sulfide complex. On addition of isocyanide **1b** and aldehyde **3a**, oxazolidines **4c** (46%) and **4d** (47%) were generated. With respect to the preparation of oxazolidine **4c**, a consideration should be made about the hydroboration: when using terminal alkenes, the regioselectivity is usually high



Scheme 2. Borane range (PMP = *p*-MeO-C_6H_4).



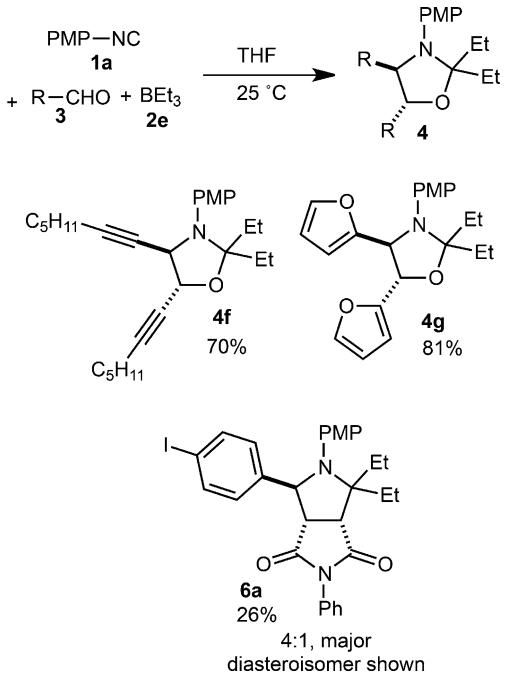
Scheme 3. Cross-over experiment with $B(Et)_3$ and $B(Bu)_3$.

(≈95%); on the other hand with phenyl-substituted alkenes, such as styrene, selectivity is described to drop to 80%.[11] Therefore a mixture of boranes results from the hydroboration of styrene, **2c** being the major species. Nevertheless oxazolidine **4c** is the only product detected in the reaction mixture (Scheme 2), suggesting also clear preferences in the boron to carbon migration step. This implies that bulky or branched organoboranes should be less reactive, and accordingly, benzyl-BBN on interaction with *p*-chlorobenzaldehyde **3a** and *p*-methoxyphenyl isocyanide **1b** did not yield any MCR adduct.

With regard to the reaction mechanism, it remained unclear whether the two alkyl groups transferred to the isocyanide terminal carbon arise from the same or different borane molecules. A cross-over experiment was designed to settle this point, and isocyanide **1b** and aldehyde **3a** were reacted with a mixture of $B(Et)_3$ and $B(Bu)_3$ to afford roughly equimolar amounts of oxazolidines **4e** and **4a** having either two ethyl or two butyl residues, but no mixed products (Scheme 3). This supports the mechanistic hypothesis previously described,[8] and demonstrates that the two alkyl groups of each oxazolidine come from the same trialkylborane reactant molecule.

The aldehyde scope is further explored, with the objective of adding more functional groups whose reactivity may enable post-condensation transformations. For instance, fused pyrrolidine **6a** (26%, Scheme 4) was readily prepared from *p*-iodobenzaldehyde, $B(Et)_3$, *N*-phenylmaleimide and *p*-methoxyphenyl isocyanide **1b**, and displays a C–I bond, suitable for metal-catalyzed couplings. Furthermore, 2-octynal is used in a 3-component process to afford the corresponding oxazolidine **4f** (70%). This constitutes a quick access to a functionalized dialkynyl moiety, suitable for metal-domino processes or as a building block for the preparation of complex structures. This compound is present in the reaction crude in high amount, but decomposes on chromatographic purification attempts; however it can be used directly in the next reaction step. With respect to heterocyclic aldehydes, furfural afforded the expected oxazolidine **4g** in 81% yield (Scheme 4).

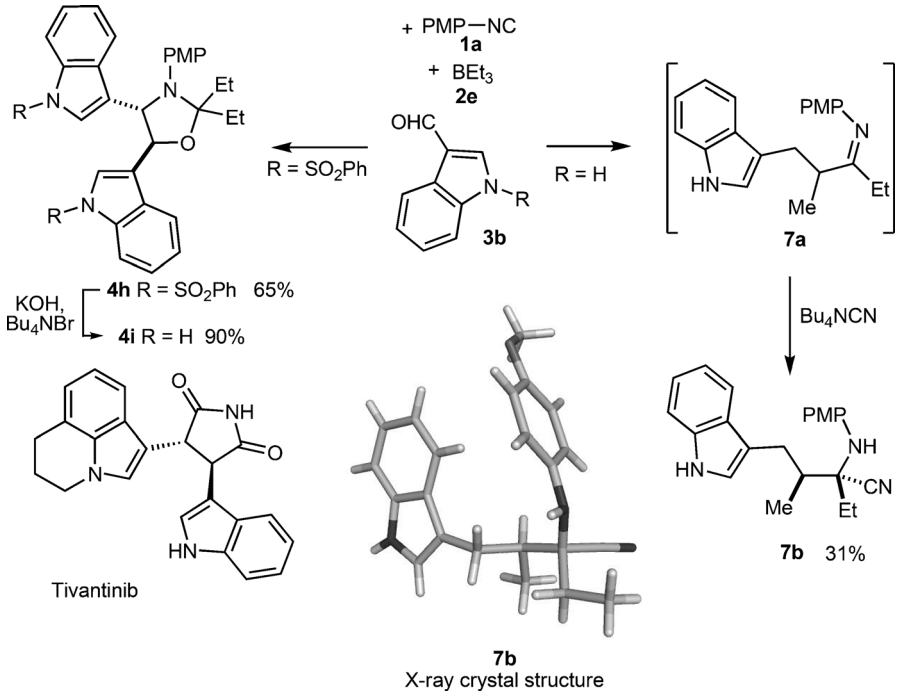
On the other hand, the reaction of indole-3-carbaldehyde (**3b**, R = H), *p*-methoxyphenyl isocyanide **1b** and $B(Et)_3$ resulted in a novel process leading to the unstable imine **7a** (70% conversion, Scheme 5) having



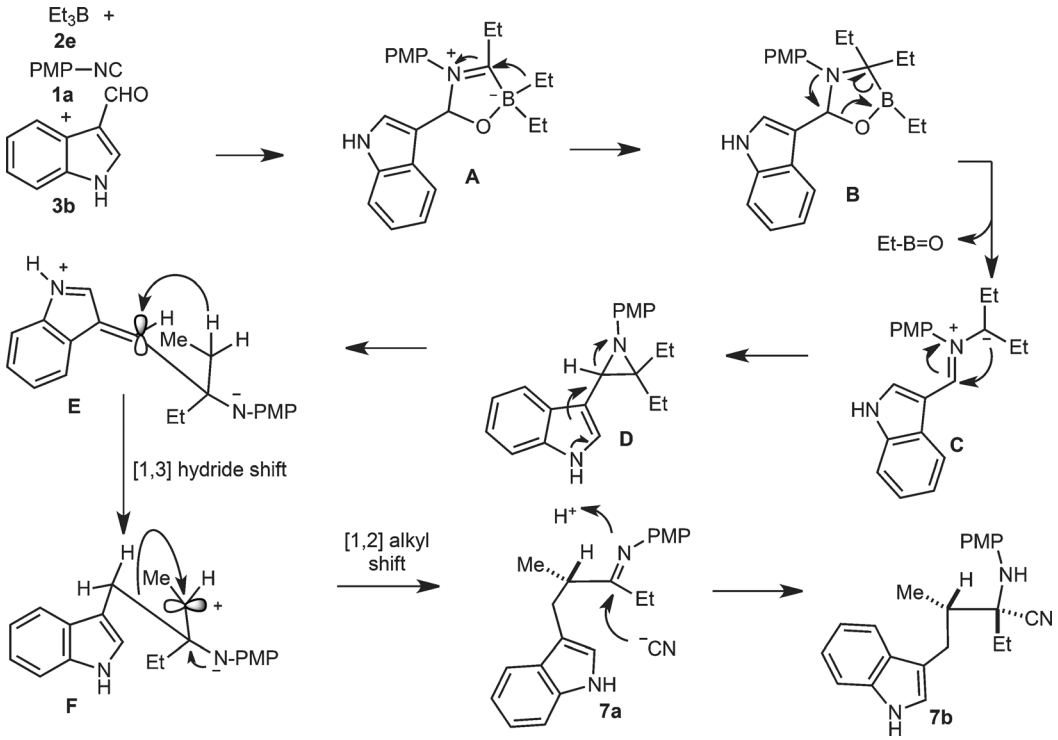
Scheme 4. New aldehydes suitable for post-condensation reactions.

the same molecular mass as the expected aziridine (**D**, Scheme 6). Although this compound could not be characterized,[12] treatment of this intermediate with tetrabutylammonium cyanide yielded the α-amino nitrile **7b** in a stereoselective manner. The structure of this compound was univocally assigned by X-ray diffraction (Scheme 5).[13] The interpretation of this remarkable result may be related to the formation of the expected aziridine, (**D**, Scheme 6), by ring closure from the azomethine ylide **C**, since electron-rich aldehydes suffer this transformation.[8] In this case, the indole-azidirine **D** is abnormally reactive[14] and suffers a gramine-type C–N bond heterolysis to give zwitterion **E** which undergoes a [1,3] hydride shift[15] to isomerize to **F** which in turn experiences a [1,2] alkyl shift[16] to finally yield the putative imine **7a**.

There is a clear thermodynamic driving force that facilitates this orchestrated rearrangement, as this imine is considerably more stable than the starting aziridine **D**.[17] The overall transformation involves the formation of three C–C bonds, the net insertion of an



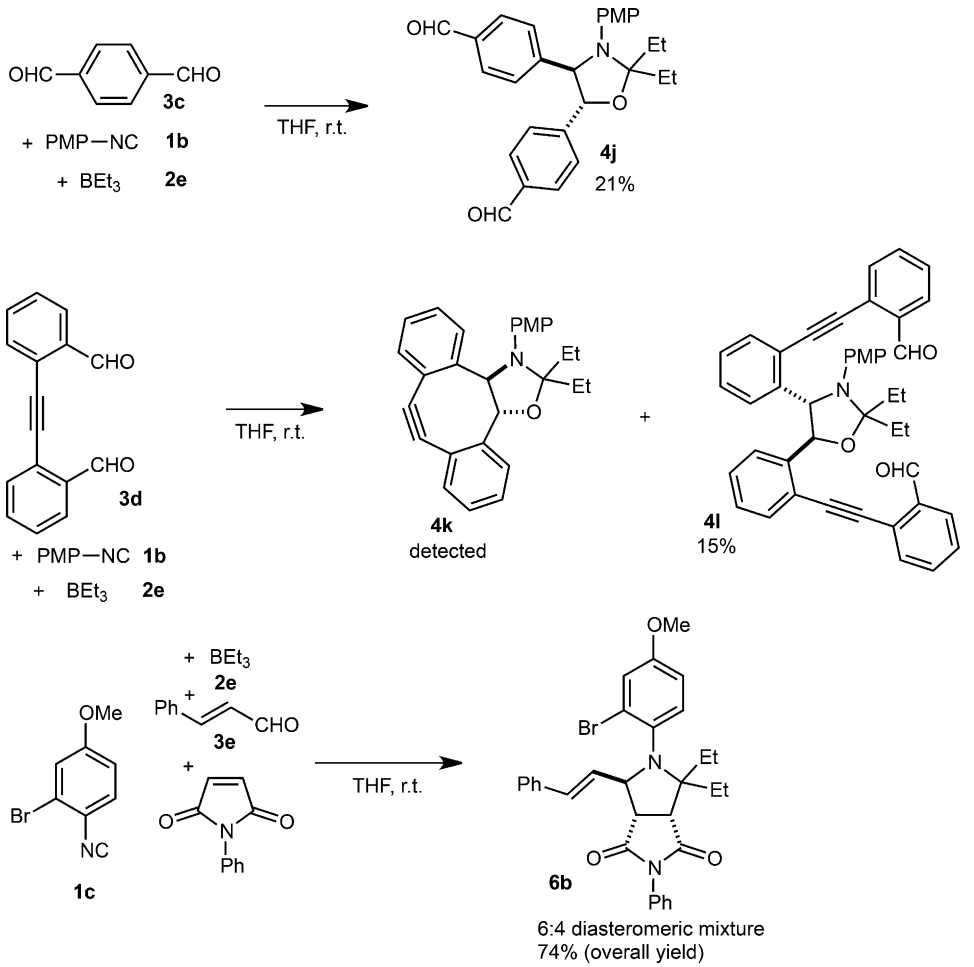
Scheme 5. Oxazolidine and aziridine nucleophilic opening.



Scheme 6. Mechanistic hypothesis for the formation of imine **7a**.

indolylmethyl moiety into an alkyl group and the differentiation of the two ethyl substituents coming from the borane component.[18] The whole process takes place in one operation, just mixing the reactants. Furthermore, the cyanide addition to the imine leads to the isolated amino nitrile in a stereoselective manner.[19] The reaction can be tuned, and when performing the transformation with the *N*-sulfonylated analogue (**3b**, R = Ph-SO_2-),[20] *trans*-oxazolidine **4h** (65%) was satisfactorily obtained (Scheme 5).

Noticeably, the electronic effect of the *N*-protecting group of the indole is able to modulate the reactivity

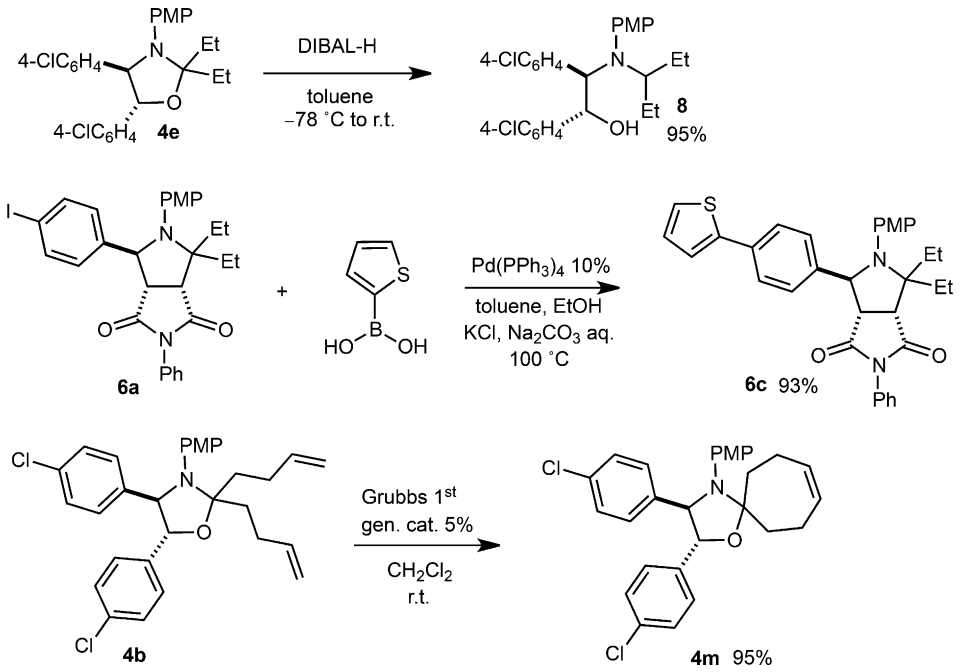


Scheme 7. MCRs of dialdehydes **3c**, **3d** and isocyanide **1c**.

of the aldehyde component, and in this way, the imine pathway was avoided, as the dipolar cycloaddition to another aldehyde unit prevailed. This compound could be deprotected with KOH under phase-transfer catalysis to yield the N–H derivative **4i** (90%),[21] thus allowing the preparation of both scaffolds from the same indole precursor. The 1,2-(3-indolyl)ethane moiety is present in relevant bioactive structures and natural products.[22] Among them, especially appealing is Tivantinib (ARQ197, Scheme 5), a new antitumoral in clinical phase III trials, that selectively targets the *c*-Met receptor tyrosine kinase, and is giving promising results against several cancers.[23] Furthermore, this chemotype is the synthetic precursor of the staurosporine-indolocarbazole class of alkaloids and is readily transformed into these compounds by acid-promoted cyclization.[24] Noteworthy, these approaches often require long sequences, whereas the preparation of derivative **4i** takes place with high step-economy.

To explore the possibility of promoting intramolecular MCRs, the use of dialdehydes is investigated. Phthaldialdehyde and isophthalaldehyde gave complex mixtures of products, in which several oxazolidine adducts can be detected. Interestingly, terephthaldehyde (**3c**) reacted in a clean way to afford the corresponding oxazolidine **4j** (21%, Scheme 7) bearing two unreacted formyl groups. Additionally, alkynedialdehyde **3d**[25] was reacted with isocyanide **1b** and $B(Et)_3$. The corresponding cyclooctyne oxazolidine **4k** was detected in trace amounts by HPLC-MS, however the dialkynyloxazolidine **4l** (15%) was the main product and could be properly purified and characterized.

With regard to new isocyanides, the *ortho*-bromo substituted isocyanide **1c** properly reacted with cinnamaldehyde (**3e**), *N*-phenylmaleimide and triethylborane to afford the fused pyrrolidine **6b** (74%, Scheme 7). On the other hand, de Meijere's *o*-isocyanophenylcarbaldehyde[26] led to complex mixtures on attempting MCRs with boranes in the presence or absence of dipolarophiles. Overall, these results confirm that the expected reactivity can be observed with several (di)substituted aldehydes and isocyanides, however the formation of small or medium rings is not fa-

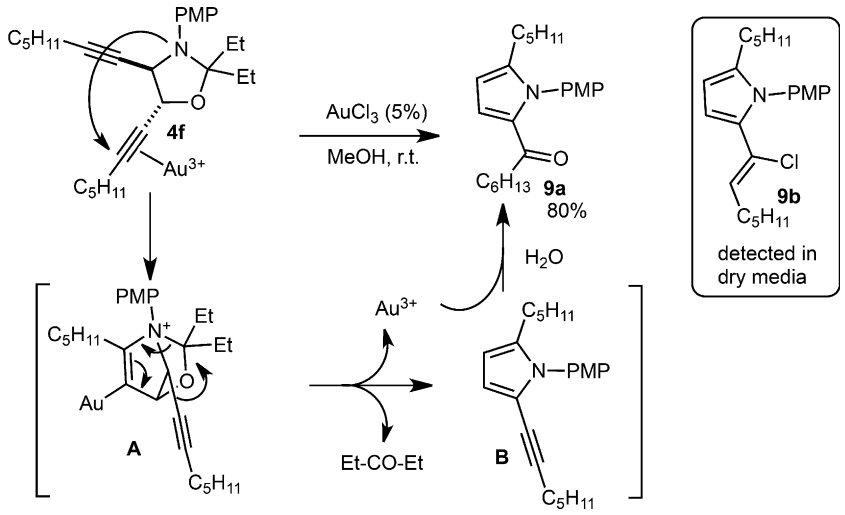


Scheme 8. Reductive opening of oxazolidines, Pd- and Ru-catalyzed post-modifications.

vored, and intermolecular pathways are largely followed in these cases.

Next we explored the possibility of performing post-condensation transformations in order to further increase the complexity of the multicomponent adducts. First, we considered the reductive opening of oxazolidines to the corresponding amino alcohols. In this way, oxazolidine **4e**[8] is reacted with DIBAL-H, to selectively yield ethanolamine **8** with conservation of the relative stereochemistry (95%, Scheme 8).[27] Next, we studied metal-catalyzed transformations. On attempting an intramolecular Heck coupling with pyrrolidine **6b**, decomposition of the starting material took place. On the other hand, pyrrolidine **6a** (Scheme 8) readily reacted with the corresponding boronic acid in a Suzuki coupling, to afford the thiophene derivative **6c** in excellent yield. Furthermore, oxazolidine **4b** readily cyclized through ring-closing metathesis using the Grubbs catalyst (1st generation) to yield the cycloheptene adduct **4m** (95%, Scheme 8), overcoming the intrinsic limitation due to the lack of reactivity of cyclic boranes.

Next, we explored a metal-catalyzed hydroamination of alkynyloxazolidine **4f**. This process was readily inducted by catalytic $AuCl_3$, triggering a complex cascade reaction and leading to the highly functionalized pyrrole **9a** (80%, Scheme 9).



Scheme 9. Au-catalyzed hydroamination-hydration of oxazolidine **4f**.

The reaction is probably initiated by activation of one triple bond by Au^{3+}, followed by the intramolecular attack of the nitrogen of the oxazolidine. Subsequent rearrangements allow the elimination of pentanone and, through proton shift and protonolysis of the Au–C bond, the generation of pyrrole **B**. At this stage the remaining triple bond undergoes a gold-catalyzed hydration, likely taking place during the final aqueous work-up, to yield the final ketopyrrole **9a**. When the reaction was performed in dry DCM with a substoichiometric source of chloride anion (from $AuCl_3$), chlorinated pyrrole **9b** was produced in small amounts. The latter compound, however, is unstable and tends to convert into oxazolidine **9a** during the work-up. Related transformations leading to pyrroles have been recently reported.[28]

Conclusions

In summary, the scope of MCRs involving trialkylboranes, isocyanides, aldehydes and dipolarophiles has been considerably expanded. The borane input can be prepared *in situ*, the aldehyde range includes α,β-unsaturated and heteroaromatic derivatives (furan, indole), and the isocyanide scope, although restricted to the aromatic series,[29] allows an *ortho* substitution. Unexpected chemistry has been found for the indole-3-carbaldehyde MCRs, leading to novel scaffolds and complex but rational mechanistic pathways. Also, the generated adducts can be further modified to yield diverse structures by simple post-condensation modifications. Thus, reductive opening leads to amino alcohols and metal-catalyzed reactions (Suzuki coupling, ring-closing metathesis, and gold-promoted hydroamination–hydration sequences) originate a variety of scaffolds in direct transformations. Although the need for the specific preparation of some boranes and scope limitations in some reactants may represent restrictions in the practical/industrial applications of this MCR, the described methodology stands as a very efficient way to access a wide family of heterocyclic compounds with relevant presence in biological and medicinal chemistry.

Experimental Section

Unless stated otherwise, all reactions were carried out under argon in dried glassware. Commercially available reactants were used without further purification. Thin-layer chromatography was conducted with Merck silica gel 60 F254 sheets and visualized by UV. Silica gel (particle size 35-70 μm) was used for flash column chromatography. ^1H and ^{13}C NMR spectra were recorded with a Varian Mercury 400 spectrometer (at 400 and 100 MHz, respectively). NMR spectra were recorded in $CDCl_3$ solution with TMS as an internal reference. Data for ^1H NMR spectra are reported as follows: chemical shift (δ/ppm), multiplicity, coupling constant (J/Hz) and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to the solvent peak of $CDCl_3$ set at $\delta = 77.0$ ppm. IR spectra were recorded with a Thermo Nicolet Nexus spectrometer and are reported in frequency of absorption (cm^{-1}). HPLC analysis were performed on a Waters Alliance 2695 separations module (Empower software) connected to a Waters PDA2996 photodiode array detection (PDA) system (190–800 nm) and using a *Symmetry* column (C18, 5 mm, 4.6×150 mm). High resolution mass spectrometry was performed by the University of Barcelona Mass Spectrometry Service.

General Procedure for Oxazolidine Synthesis

A solution of isocyanide (1 mmol, 1 equiv.) and aldehyde (2 mmol, 1 equiv.) in THF (2 mL) was added slowly into a solution of trialkylborane in THF (1 M, 1.2 mmol, 1.2 equiv.) at 0 °C. After 3 min stirring at this temperature, the ice bath was removed and the reaction mixture was stirred for 24 h at room temperature. An aqueous saturated solution of Na_2CO_3 (10 mL) was added and the mixture was extracted with dichloromethane (2×5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to yield the oxazolidine **4**.

General Procedure for Pyrrolidine Synthesis

A solution of isocyanide (1 mmol, 1 equiv.) and aldehyde (1 mmol, 1 equiv.) in THF (2 mL) was added slowly into a solution of trialkylborane in THF (1 M, 1.2 mmol, 1.2 equiv.) at −10 °C. Subsequently *N*-phenylmaleimide was added to the mixture. After 3 min stirring at this temperature, the cooling bath was removed and the reaction was stirred for 24 h at room temperature. An aqueous saturated solution of Na_2CO_3 (10 mL) was added and the mixture was extracted with dichloromethane (2×5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to yield the adduct **6**.

General Procedure for the Preparation of Trialkylboranes by Hydroboration

The corresponding olefin (4.0 mmol) was slowly added into a solution of $BH_3{\cdot}SMe_2$ (123 μL, 1.2 mmol) in toluene (1 mL). The solution was stirred overnight at room temperature. Afterwards THF (2 mL) was added and the solution was directly used in the next step.

(4*RS*,5*RS*)-2,2-Di(but-3-enyl)-4,5-bis(4-chlorophenyl)-3-(4-methoxyphenyl)oxazolidine (4b)

Prepared as described in the general experimental for oxazolidine synthesis. after preparation the borane solution $BF_3{\cdot}Et_2O$ (185 μL, 1.5 mmol) was added to a suspension of Mg turnings (138 mg, 5.68 mmol) and a crystal of iodine in Et_2O (4 mL). The reaction was initiated by addition of neat 4-bromobutene followed by a slow addition (1 h) of a solu-

tion of 4-bromobutene (523 μL, 5.2 mmol) in Et_2O (2 mL). The mixture was heated to reflux for 2 h, and then cooled to 0 °C. The solid was left to deposit on the bottom while the solution was transferred into a round bottom flask using a cannula and used in the next step (general experimental procedure for oxazolidine synthesis). Obtained as an amorphous solid; isolated yield: 32%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.5 Hz, 2H), 6.77 (d, J = 9.1 Hz, 2H), 6.69 (d, J = 9.1 Hz, 2H), 6.06–5.94 (m, J = 16.8, 10.2, 6.6 Hz, 1H), 5.78–5.66 (m, J = 16.9, 10.2, 6.6 Hz, 1H), 5.18 (dd, J = 17.1, 1.7 Hz, 1H), 5.05 (dd, J = 10.2, 1.6 Hz, 1H), 4.95–4.87 (m, 2H), 4.77 (d, J = 8.6 Hz, 1H), 4.46 (d, J = 8.7 Hz, 1H), 3.70 (s, 3H), 2.82–2.71 (m, J = 18.3, 8.6, 5.3 Hz, 1H), 2.54–2.42 (m, 1H), 2.30–2.04 (m, 4H), 1.91–1.82 (m, J = 14.1, 11.2, 5.0 Hz, 1H), 1.73–1.64 (m, J = 14.0, 11.1, 5.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.88, 138.70, 138.54, 136.64, 136.49, 135.93, 134.26, 133.55, 129.08, 128.90, 128.71, 128.34, 122.35, 114.86, 114.65, 114.26, 99.18, 85.70, 70.72, 55.45, 39.92, 36.95, 28.69, 28.12; IR (NaCl): ν_{max} = 2936, 2834, 1640, 1597, 1516, 1490, 1441, 1246, 1090, 1013, 912, 828 cm^{-1}; MS (EI): m/z (%) = 507 (M^+, 26), 456 (30), 455 (43), 454 (100), 453 (63), 452 (100), 372 (77), 370 (100), 245 (31) 234 (15), 232 (46), 178 (25), 166 (17), 135 (100), 122 (32), 107 (18), 55 (38); HR-MS: m/z = 508.1808, calcd. for $C_{30}H_{32}Cl_2NO_2^+$: 508.1805.

(4*RS*,5*RS*)-4,5-Bis(4-chlorophenyl)-3-(4-methoxyphenyl)-2,2-diphenethyloxazolidine (4c)

Prepared as described in the general experimental procedure for oxazolidine synthesis. The borane component was prepared from styrene following the general procedure for the preparation of trialkylboranes by hydroboration. Obtained as an amorphous solid; isolated yield: 46%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.32 (m, 6H), 7.27–7.21 (m, 4H), 7.21–7.15 (m, J = 10.5, 5.4, 3.1 Hz, 4H), 7.10 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 7.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 6.74 (d, J = 9.0 Hz, 2H), 4.89 (d, J = 8.7 Hz, 1H), 4.57 (d, J = 8.7 Hz, 1H), 3.72 (s, 3H), 3.38–3.29 (m, J = 12.8, 4.3 Hz, 1H), 3.07–2.97 (m, J = 13.0, 4.9 Hz, 1H), 2.80–2.62 (m, 1H), 2.61–2.49 (m, 2H), 2.47–2.36 (m, 1H), 2.21–2.10 (m, 1H), 2.09–1.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.87, 142.34, 142.20, 136.74, 136.31, 135.89, 134.43, 133.64, 129.04, 128.96, 128.81, 128.76, 128.64, 128.58, 128.45, 128.43, 126.16, 126.01, 122.02, 114.43, 99.19, 85.73, 70.99, 55.55, 43.49, 39.77, 31.00, 30.22; IR (NaCl): ν_{max} = 3025, 2933, 1601, 1510, 1491, 1453, 1245, 1080, 1040, 700 cm^{-1}; MS (EI): m/z (%) = 607 (M^+, 10), 504 (70), 502 (100), 372 (25), 370 (39), 244 (13), 238 (18), 231 (17), 204 (14); HR-MS: m/z = 608.2115, calcd. for $C_{38}H_{36}Cl_2NO_2^+$: 608.2118.

(4*RS*,5*RS*)-4,5-Bis(4-chlorophenyl)-2,2-dihexyl-3-(4-methoxyphenyl)oxazolidine (4d)

Prepared as described in the general experimental procedure for oxazolidine synthesis. The borane component was prepared from hexene following the general procedure for the preparation of trialkylboranes by hydroboration. Obtained as an amorphous solid; isolated yield: 46%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 9.2 Hz, 2H), 6.68 (d, J = 9.2 Hz, 2H), 4.75 (d, J = 8.6 Hz, 1H), 4.44 (d, J = 8.6 Hz, 1H), 3.70 (s, 2H), 2.20–2.10 (m, 1H), 2.01 (dd, J = 15.1, 11.1 Hz, 2H), 1.79 (ddd, J = 14.1, 12.0, 4.1 Hz, 1H), 1.69–1.57 (m, 2H), 1.48–1.35 (m, 7H), 1.28 (d, J = 6.8 Hz, 3H), 1.24–1.12 (m, 6H), 0.93 (t, J = 7.0 Hz, 3H), 0.84 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.38, 137.18, 136.71, 136.39, 134.15, 133.39, 129.03, 128.84, 128.64, 128.41, 121.70, 114.12, 100.04, 85.54, 70.87, 55.47, 41.50, 37.44, 32.20, 31.73, 29.93, 29.70, 24.41, 23.28, 22.94, 22.62, 14.30, 14.19; IR (NaCl): ν_{max} = 2929, 2858, 1510, 1496, 1441, 1284, 1245, 1189, 1040, 1014, 829 cm^{-1}; MS (EI): m/z (%) = 567 (M^+, 18), 482 (100), 370 (93), 231 (41), 178 (18), 134 (100), 122 (26), 107 (14), 77 (13); HR-MS: m/z = 568.2732, calcd. for $C_{34}H_{44}Cl_2NO_2^+$: 568.2744.

(3a*RS*,6*SR*,6a*SR*)-4,4-Diethyl-6-(4-iodophenyl)-5-(4-methoxyphenyl)-2-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6a)

Prepared as described in general experimental procedure for pyrrolidine synthesis. Obtained as an amorphous solid; isolated yield: 26%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.44 (m, 2H), 7.39 (q, J = 7.5 Hz, 2H), 7.34–7.21 (m, 3H), 7.15–7.09 (m, 2H), 6.89–6.83 (m, 2H), 6.64–6.57 (m, 2H), 5.09 (d, J = 6.7 Hz, 1H), 3.61 (s, 3H), 3.53 (d, J = 10.4 Hz, 1H), 3.23 (dd, J = 10.3, 6.6 Hz, 1H), 2.06–1.95 (m, 1H), 1.90–1.78 (m, 2H), 1.70–1.58 (m, 1H), 1.23 (t, J = 7.3 Hz, 3H), 0.54 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 175.6, 155.6, 142.3, 137.8, 137.2, 134.3, 129.3, 129.3, 128.8, 126.3, 126.2, 125.4, 113.9, 92.9, 71.7, 65.4, 55.3, 52.2, 33.4, 25.3, 9.5, 8.9; IR (NaCl): ν_{max} = 3057, 2969, 2881, 2821, 1777, 1707, 1591, 1507, 1374, 1246, 1169, 1034, 963, 823, 695 cm^{-1}; MS (EI): m/z (%) = 581 (MH^+, 35), 486 (60), 419 (43), 377 (11), 318 (100), 309 (65), 288 (63), 165 (5), 124 (6); HR-MS: m/z = 581.1299, calcd. for $C_{29}H_{30}IN_2O_3^+$: 581.1296.

(4*RS*,5*RS*)-2,2-Diethyl-4,5-di(hept-1-ynyl)-3-(4-methoxyphenyl)oxazolidine (4f)

Prepared as described in general experimental procedure for oxazolidine synthesis using 2-octynal as aldehyde component. **4f** decomposes on silica. Obtained as a dark oil; conversion: 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (d, J = 9.1 Hz, 2H), 6.81 (d, J = 9.2 Hz, 2H), 4.77 (dt, J = 8.3, 1.8 Hz, 1H), 4.38 (dt, J = 8.3, 1.8 Hz, 1H), 3.77 (s, 3H), 2.26 (td, J = 7.1, 1.7 Hz, 2H), 2.11 (td, J = 6.9, 1.8 Hz, 2H), 2.00–1.90 (m, 1H), 1.85 (dt, J = 13.1, 6.7 Hz, 1H), 1.75 (dt, J = 14.5, 7.2 Hz, 1H), 1.61–1.51 (m, 3H), 1.46–1.17 (m, 10H), 1.05 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H), 0.84 (t, J = 7.1 Hz, 3H), 0.68 (t, J = 7.3 Hz, 3H); MS (EI): m/z (%) = 423 (M^+, 2), 395 (5), 394 (18), 338 (9), 337 (21), 282 (6), 281 (12), 280 (55), 231 (18), 134 (6); HR-MS: m/z = 423,3130, calcd. for $C_{28}H_{41}NO_2^+$: 423,3137.

(4*RS*,5*RS*)-2,2-Diethyl-4,5-di(furan-2-yl)-3-(4-methoxyphenyl)oxazolidine (4g)

Prepared as described in the general experimental procedure for oxazolidine synthesis using furfural as aldehyde component. Obtained as an amorphous solid; isolated yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.46 (m, J = 1.8, 0.8 Hz, 1H), 7.26–7.25 (m, J = 1.8, 0.8 Hz, 1H), 6.87 (d, J =

9.1 Hz, 2H), 6.74 (d, $J=9.1$ Hz, 2H), 6.42–6.40 (m, $J=3.3$, 0.7 Hz, 1H), 6.38–6.35 (m, $J=3.3$, 1.8 Hz, 1H), 6.22–6.19 (m, $J=3.2$, 1.8 Hz, 1H), 6.18–6.16 (m, $J=3.3$, 0.7 Hz, 1H), 5.18 (s, 2H), 3.73 (s, 3H), 2.14–1.96 (m, 2H), 1.91–1.80 (m, 1H), 1.65–1.56 (m, 1H), 1.25 (t, $J=7.4$ Hz, 3H), 0.80 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=154.17$, 152.11, 151.06, 143.34, 142.15, 137.58, 120.79, 114.07, 110.43, 110.38, 109.57, 108.00, 100.66, 77.03, 61.51, 55.49, 34.31, 29.96, 8.62, 7.60; IR (NaCl): $\nu_{max}=2950$, 2875, 1593, 1490, 1472, 1329, 1254, 1122, 1087, 995, 841, 811 cm^{-1}; MS (EI): m/z (%) = 368 (MH^+, 90), 310 (5), 282 (100), 272 (27), 269 (5), 142 (10), 104 (5), 102 (9); HR-MS: $m/z=368.1861$, calcd. for $C_{22}H_{26}NO_4^+$: 368.1856.

(4*RS*,5*RS*)-2,2-Diethyl-3-(4-methoxyphenyl)-4,5-bis[1-(phenylsulfonyl)-1*H*-indol-3-yl]oxazolidine (4h)

Prepared as described in the general experimental procedure for oxazolidine synthesis, using 1-(phenylsulfonyl)-1*H*-indole-3-carbaldehyde as aldehyde component. Obtained as an amorphous solid; isolated yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.86$ (d, $J=8.4$ Hz, 1H), 7.76–7.70 (m, 3H), 7.49–7.42 (m, 2H), 7.40–7.30 (m, 6H), 7.20–7.11 (m, 3H), 7.05–6.96 (m, 2H), 6.85–6.79 (m, 1H), 6.76–6.70 (m, 2H), 6.71–6.60 (m, 2H), 6.60–6.54 (m, 2H), 5.19 (d, $J=8.7$ Hz, 1H), 5.01 (d, $J=8.8$ Hz, 1H), 3.66 (s, 3H), 2.22–2.10 (m, 1H), 2.06–1.94 (m, 1H), 1.88–1.77 (m, 1H), 1.64–1.53 (m, 1H), 1.28 (t, $J=7.3$ Hz, 3H), 0.87 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=154.8$, 138.2, 137.6, 137.1, 135.4, 135.3, 134.0, 133.6, 129.8, 129.5, 129.2, 128.9, 126.9, 126.5, 125.6, 125.0, 124.8, 124.7, 123.3, 123.2, 122.7, 120.3, 120.23, 120.20, 119.7, 114.1, 113.8, 113.7, 99.9, 79.1, 62.0, 55.4, 32.9, 30.1, 8.9, 8.3; IR (NaCl): $\nu_{max}=3058$, 2975, 2937, 2879, 3058, 1444, 1367, 1175 cm^{-1}; MS (EI): m/z (%) = 745 (M^+, 100), 410 (68), 300 (22), 142 (46), 101 (66); HR-MS: $m/z=746.2353$, calcd. for $C_{42}H_{40}N_3O_6S_2$ ($M+H^+$): 746.2346.

(4*RS*,5*RS*)-2,2-Diethyl-4,5-di(1*H*-indol-3-yl)-3-(4-methoxyphenyl)oxazolidine (4i)

This deprotection step was accomplished through a modified version of Liu's procedure.[21] Tetrabutylammonium bromide (86 mg, 268 μmol) and KOH (15 mg, 286 μmol) were added to a solution of oxazolidine **4h** (20 mg, 27 μmol) in THF (0.5 mL) and H_2O (0.2 mL). The mixture was refluxed at 65 °C until completion of the reaction (3 h). Water (5 mL) was added and the mixture was extracted with ethyl acetate (2×5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to yield the oxazolidine **4i** as an amorphous solid; isolated yield: 12 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.86$ (br. 1H), 7.78 (br, 1H), 7.53 (d, $J=7.9$ Hz, 1H), 7.28–7.21 (m, 2H), 7.18–7.10 (m, 2H), 7.05–6.99 (m, 2H), 6.94–6.87 (m, 2H), 6.87–6.77 (m, 3H), 6.69–6.61 (m, 2H), 5.39 (d, $J=9$ Hz, 1H), 5.33 (d, $J=9$ Hz, 1H), 3.64 (s, 3H), 2.34–2.23 (m, 1H), 2.22–2.10 (m, 1H), 2.05–1.94 (m, 1H), 1.76–1.64 (m, 1H), 1.38 (t, $J=7.3$ Hz, 3H), 0.96 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=153.9$, 138.5, 136.8, 136.4, 126.6, 126.2, 124.1, 123.5, 122.1, 121.69, 121.66, 120.10, 119.9, 119.7, 119.2, 113.9, 113.6, 113.4, 111.3, 111.1, 99.4, 80.2, 62.1, 55.4, 33.3, 29.9, 9.1, 8.2; IR (NaCl): $\nu_{max}=2920$, 2734, 1772, 1550, 1595, 1421, 1374, 934, 647 cm^{-1}; HR-MS: $m/z=466.2491$, calcd for $C_{30}H_{32}N_3O_2$ ($M+H^+$): 466.2489.

(2*RS*,3*RS*)-2-Ethyl-4-(1*H*-indol-3-yl)-2-(4-methoxyphenylamino)-3-methylbutanenitrile (7b)

A cold solution of triethylborane in THF (1 M, 1.2 mL, 1.2 mmol) was added dropwise onto a mixture of 4-methoxyphenyl isocyanide (133 mg, 1 mmol) and indole-3-carbaldehyde (145 mg, 1 mmol) in THF (2 mL) at 0 °C. After 10 min the ice bath was removed and the mixture was stirred under nitrogen overnight. A solution of tetrabutylammonium cyanide (403 mg, 1.5 mmol) in MeOH (5 mL) was added and the mixture was stirred for 16 h at room temperature. Water (10 mL) was added and the mixture was extracted with Et_2O (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to afford amino nitrile **7b** as a white solid; isolated yield: 142 mg (31%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.97$ (s, 1H), 7.34 (d, $J=8.2$ Hz, 1H), 7.24–7.13 (m, 2H), 7.07–6.97 (m, 3H), 6.94 (s, 1H), 6.87 (d, $J=8.9$ Hz, 2H), 3.81 (s, 3H), 3.49 (s, 1H), 3.22 (d, $J=12.7$ Hz, 1H), 2.53 (s, 2H), 2.01 (s, 1H), 1.92 (s, 1H), 1.19 (t, $J=7.4$ Hz, 3H), 1.08 (d, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=157.65$, 139.57, 137.53, 135.71, 133.44, 133.08, 131.46, 130.85, 128.85, 128.23, 127.86, 113.88, 73.55, 72.79, 67.37, 55.52, 25.98, 25.21, 11.49, 11.35 ppm. IR (NaCl) $\nu_{max}=2911$, 2743, 1764, 1563, 1515, 1462, 1344, 661 cm^{-1}; MS (EI): m/z (%) = 458 (M^+, 100), 310 (8), 424 (5), 318 (14), 316 (23), 282 (7), 208 (13), 194 (8), 102 (10); HR-MS: $m/z=458.1650$, calcd. for $C_{26}H_{30}Cl_2NO_2^+$: 458.1648.

4,4′-[(4*RS*,5*RS*)-2,2-Diethyl-3-(4-methoxyphenyl)-oxazolidine-4,5-diyl]dibenzaldehyde (4j)

Prepared as described in the general experimental procedure for oxazolidine synthesis using terephthaldehyde as aldehyde component. Obtained as an amorphous solid; isolated yield: 21%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=10.02$ (s, 1H), 9.93 (s, 1H), 7.84 (d, $J=8.1$ Hz, 2H), 7.73 (d, $J=8.1$ Hz, 2H), 7.33 (t, $J=7.4$ Hz, 4H), 6.78 (d, $J=9.0$ Hz, 2H), 6.68 (d, $J=9.0$ Hz, 2H), 4.95 (d, $J=8.7$ Hz, 1H), 4.63 (d, $J=8.7$ Hz, 1H), 3.68 (s, 3H), 2.31–2.20 (m, 1H), 2.14–2.03 (m, 1H), 1.95–1.84 (m, 1H), 1.75–1.64 (m, 1H), 1.33 (t, $J=7.3$ Hz, 3H), 0.95 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=191.81$, 191.68, 154.57, 144.74, 144.69, 136.62, 136.45, 136.15, 129.98, 129.76, 128.29, 127.37, 121.80, 114.06, 100.68, 85.54, 71.20, 55.26, 33.02, 29.88, 8.64, 7.99; IR (NaCl): $\nu_{max}=2934$, 2834, 2735, 1701, 1608, 1578, 1463, 1246, 1206, 1037, 947, 815 cm^{-1}; MS (EI): m/z (%) = 444 (MH^+, 52), 414 (45), 358 (91), 269 (10), 239 (15), 191 (58), 129 (24), 121 (100); HR-MS: $m/z=444.2172$, calcd. for $C_{28}H_{30}NO_4^+$: 444.2169.

2,2′-{2,2′-[(4*RS*,5*RS*)-2,2-Diethyl-3-(4-methoxyphenyl)oxazolidine-4,5-diyl]bis(2,1-phenylene)}bis-(ethyne-2,1-diyl)dibenzaldehyde (4l)

Prepared as described in the general experimental procedure for oxazolidine synthesis using 2,2′-(ethyne-1,2-diyl)di-

benzaldehyde as aldehyde component. Obtained as an amorphous solid; isolated yield: 15%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.27 (d, J = 0.6 Hz, 1H), 10.21 (d, J = 0.7 Hz, 1H), 7.83 (m, J = 14.0, 7.8, 1.4 Hz, 2H), 7.78–7.74 (m, 1H), 7.65–7.60 (m, 1H), 7.47 (m, J = 17.6, 7.5, 1.4 Hz, 2H), 7.41–7.33 (m, 2H), 7.33–7.27 (m, 2H), 7.24 (dd, J = 7.7, 1.2 Hz, 2H), 6.98–6.93 (m, 2H), 6.77–6.71 (m, 3H), 6.71–6.66 (m, 1H), 6.65–6.59 (m, 2H), 5.53 (d, J = 8.7 Hz, 1H), 5.24 (d, J = 8.7 Hz, 1H), 3.60 (s, 3H), 2.28–2.16 (m, 1H), 2.14–2.02 (m, 1H), 1.95–1.83 (m, 1H), 1.74–1.62 (m, 1H), 1.34 (t, J = 7.3 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.64, 191.51, 154.31, 140.47, 140.00, 137.42, 135.59, 135.50, 133.63, 133.54, 133.36, 133.25, 132.46, 132.34, 130.00, 129.65, 128.62, 128.51, 128.11, 127.56, 127.36, 126.95, 126.71, 122.35, 121.63, 121.46, 114.24, 100.30, 93.94, 93.82, 89.28, 88.45, 83.45, 68.62, 55.42, 33.54, 31.74, 30.21, 22.80, 14.27, 8.90, 8.20; IR: (NaCl): ν_{max} = 3065, 2975, 2924, 2824, 2834, 2738, 1700, 1597, 1508, 1245 cm^{-1}; HR-MS: m/z = 644.2791, calcd, for $C_{44}H_{38}NO_4$ ($M+H^+$): 644.2795.

(3a*RS*,6*SR*,6a*SR*)-5-(2-Bromo-4-methoxyphenyl)-4,4-diethyl-2-phenyl-6-styryltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6b)

Prepared as described in the general experimental procedure for pyrrolidine synthesis. Obtained as an amorphous solid; overall yield: 74% (minor diastereomer of a 6:4 mixture described). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.48 (m, J = 7.6 Hz, 2H), 7.44–7.40 (m, J = 7.5 Hz, 1H), 7.40–7.35 (m, J = 7.2 Hz, 2H), 7.26 (s, 1H), 7.21–7.18 (m, J = 4.3 Hz, 3H), 7.18–7.14 (m, 2H), 7.07 (d, J = 2.9 Hz, 1H), 6.76 (dd, J = 8.8, 2.9 Hz, 1H), 6.39 (d, J = 15.7 Hz, 1H), 6.04 (dd, J = 15.7, 9.2 Hz, 1H), 4.50 (dd, J = 9.0, 7.7 Hz, 1H), 3.72 (s, 3H), 3.49 (t, J = 7.7 Hz, 1H), 3.34 (d, J = 7.8 Hz, 1H), 2.30–2.18 (m, 1H), 1.99–1.89 (m, 2H), 1.88–1.78 (m, J = 14.4, 7.3 Hz, 1H), 1.04 (t, J = 7.3 Hz, 3H), 0.46 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ =)176.13, 175.27, 158.23, 136.83, 135.70, 134.20, 132.48, 130.57, 129.78, 129.36, 128.68, 128.43, 127.60, 127.24, 126.92, 126.86, 117.89, 113.86, 71.06, 66.58, 55.58, 51.01, 48.83, 26.97, 22.71, 9.57, 8.09; IR (NaCl): ν_{max} = 2881, 1774, 1710, 1597, 1493, 1384, 1285, 1220, 1916, 966, 736, 639 cm^{-1}; MS (EI): m/z (%) = 559 (MH^+, 43), 513 (20), 502 (9), 483 (10), 473 (7), 201 (15), 141 (43), 137 (45), 122 (100); HR-MS: m/z = 559.1581, calcd. for $C_{31}H_{32}BrN_2O_3^+$: 559.1591.

(1*RS*,2*RS*)-1,2-Bis(4-chlorophenyl)-2-[(4-methoxyphenyl)(pentan-3-yl)amino]ethanol (8)

A solution of DIBAL-H in heptanes (1M, 383 μL, 383 μmol) was added dropwise in 10 min into a solution of oxazolidine **4e** (45 mg, 110 μmol) in dry toluene (0.7 mL) at −78 °C under nitrogen. The solution was allowed to slowly reach room temperature and stirred overnight. Ethyl acetate (10 mL) and a saturated water solution of sodium potassium tartrate (10 mL) were added and the mixture stirred for a further 30 min. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to yield amino alcohol **8** as an oil; isolated yield: 48 mg (95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, J = 8.5 Hz, 2H), 7.01 (t, J = 8.8 Hz, 4H), 6.89 (d, J = 9.0 Hz, 2H), 6.79 (d, J = 9.0 Hz, 2H), 6.53 (d, J = 8.5 Hz, 2H), 5.13 (s, 1H), 4.65 (d, J = 9.8 Hz, 1H), 4.05 (d, J = 9.8 Hz, 1H), 3.82 (s, 3H), 3.01–2.93 (m, 1H), 1.62–1.48 (m, 3H), 1.43–1.31 (m, J = 14.2, 7.3 Hz, 1H), 0.99 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.65, 139.57, 137.53, 135.71, 133.44, 133.08, 131.46, 130.85, 128.85, 128.23, 127.86, 113.88, 73.55, 72.79, 67.37, 55.52, 25.98, 25.21, 11.49, 11.35; IR (NaCl): ν_{max} = 2931, 2874, 1703, 1595, 1569, 1463, 1383, 1246, 1091, 1013, 830, 746 cm^{-1}; MS (EI): m/z (%) = 458 (M^+, 100), 310 (8), 424 (5), 318 (14), 316 (23), 282 (7), 208 (13), 194 (8), 102 (10); HR-MS: m/z = 458.1650, calcd. for $C_{26}H_{30}Cl_2NO_2^+$: 458.1648.

(3a*RS*,6*SR*,6a*SR*)-4,4-Diethyl-5-(4-methoxyphenyl)-2-phenyl-6-[4-(thiophen-2-yl)phenyl]tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (6c)

A Schlenk vessel was charged with pyrrolidine **6a** (150 mg, 258 μmol), 2-thienylboronic acid (43 mg, 336 μmol), and KCl (58 mg, 775 μmol). After three argon/vacuum cycles, toluene (3 mL) and ethanol (0.8 mL) were added followed by a 2M water solution of Na_2CO_3 (1.29 mL, 2.58 mmol). After three argon/vacuum cycles, the mixture was stirred for 10 min, then $Pd(PPh_3)_4$ (10%, 30 mg, 26 μmol) was added quickly under a flow of argon. Three more argon/vacuum cycles were made, and the mixture was stirred at 100 °C overnight. The mixture was cooled to room temperature and filtered through a celite pad, washing with ethyl acetate. The resulting solution was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to yield the thiophene derivative **6c** as an amorphous solid; isolated yield; 129 mg (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, J = 6.9 Hz, 5H), 7.39–7.29 (m, 2H), 7.29–7.22 (m, 2H), 7.18–7.11 (m, 2H), 6.95 (dd, J = 5.1, 3.6 Hz, 1H), 6.90 (d, J = 9.0 Hz, 2H), 6.61 (d, J = 9.0 Hz, 2H), 5.16 (d, J = 6.6 Hz, 1H), 3.61 (s, 3H), 3.56 (d, J = 10.4 Hz, 1H), 3.31 (dd, J = 10.3, 6.6 Hz, 1H), 2.07–1.98 (m, 1H), 1.87 (s, 2H), 1.73–1.62 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.57 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.87, 175.80, 155.47, 144.26, 141.86, 137.51, 133.56, 131.96, 129.33, 128.77, 128.05, 127.73, 126.40, 126.30, 125.27, 124.72, 123.03, 113.89, 71.70, 65.62, 55.33, 52.33, 52.14, 33.56, 25.39, 9.51, 8.99; IR: (NaCl): ν_{max} = 3064, 2962, 2930, 2879, 2251, 1777, 1706, 1591, 1501 cm^{-1}, HR-MS: m/z = 537.2210, calcd. for $C_{33}H_{33}N_2O_3S$ ($M+H^+$): 537.2206.

(2*RS*,3*RS*)-2,3-Bis(4-chlorophenyl)-4-(4- methoxyphenyl)-1-oxa-4-azaspiro[4.6]undec-8-ene (4m)

A solution of oxazolidine **4b** (40 mg, 79 μmol) in dichloromethane (15 mL) was treated with $Cl_2(PCy_3)_2Ru{=}CHPh$ (5%, 3 mg, 4 μmol) and stirred overnight at room temperature. The mixture was filtered through a celite pad washing with dichloromethane. The solvent was evaporated in vacuum and the resulting residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate). Obtained as an amorphous solid; isolated yield: 36 mg (95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, J = 8.4 Hz, 2H), 7.15 (d, J =

8.4 Hz, 2H), 7.11 (d, $J=8.3$ Hz, 2H), 7.06 (d, $J=8.5$ Hz, 2H), 6.89 (d, $J=9.0$ Hz, 2H), 6.68 (d, $J=9.0$ Hz, 2H), 5.88–5.74 (m, 2H), 4.78 (d, $J=8.5$ Hz, 1H), 4.41 (d, $J=8.5$ Hz, 1H), 3.69 (s, 3H), 2.54–2.44 (m, 1H), 2.43–2.31 (m, 2H), 2.22–2.04 (m, 2H), 1.99–1.86 (m, 1H), 1.86–1.78 (m, $J=11.8$, 7.0, 1.3 Hz, 1H), 1.63–1.55 (m, $J=13.6$, 9.1, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=155.65$, 136.73, 136.68, 135.84, 134.05, 133.41, 132.27, 132.24, 129.29, 128.72, 128.60, 128.35, 124.62, 114.04, 99.34, 84.42, 71.12, 55.41, 41.03, 37.21, 23.32, 22.27; IR (NaCl): $\nu_{max}=2933$, 2834, 1598, 1510, 1490, 1284, 1244, 1180, 1132, 1076, 1039, 1013, 828 cm^{-1}; MS (EI): *m/z* (%) = 480 (M^+, 100), 454 (25), 447 (28), 410 (68), 370 (35), 320 (35), 300 (22), 142 (46), 101 (66); HR-MS: *m/z* = 480.1476, calcd. for $C_{28}H_{28}Cl_2NO_2^+$: 480.1492.

1-[1-(4-Methoxyphenyl)-5-pentyl-1*H*-pyrrol-2-yl]-heptan-1-one (9a)

A solution of oxazolidine **4f** (50 mg, 118 μmol) in MeOH (1 mL) was treated with $AuCl_3$ (5%, 1.8 mg, 6 μmol). After 5 h stirring at room temperature ethyl acetate (5 mL) and a saturated solution of Na_2CO_3 (5 mL) were added. The layers were separated and the aqueous phase was extracted with ethyl acetate (2×5 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was evaporated under vacuum and the residue was purified by column chromatography (SiO_2, Hexanes/Ethyl acetate). Obtained as an amorphous solid; isolated yield: 34 mg (80%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.10$–7.04 (m, $J=8.0$, 4.0 Hz, 2H), 7.02 (d, $J=4.0$ Hz, 1H), 6.97–6.91 (m, $J=8.0$, 4.0 Hz, 2H), 6.06 (d, $J=3.9$ Hz, 1H), 3.85 (s, 3H), 2.68 (t, $J=8.0$ Hz, 2H), 2.29 (t, $J=8.0$ Hz, 2H), 1.64–1.54 (m, 2H), 1.48 (m, $J=14.9$, 7.4 Hz, 2H), 1.34–1.19 (m, 10H), 0.88–0.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=189.75$, 159.15, 144.28, 132.67, 132.07, 128.74, 119.01, 114.18, 107.17, 55.59, 39.15, 31.91, 31.63, 29.33, 28.50, 26.70, 25.22, 22.74, 22.53, 14.27, 14.11; IR (NaCl): $\nu_{max}=2955$, 2858, 1652, 1609, 1600, 1465, 1377, 1249, 1170, 1107, 1032, 833 cm^{-1}; MS (EI): *m/z* (%) = 355 (M^+, 32), 298 (22), 286 (21), 285 (100), 270 (49), 228 (18), 186 (17), 164 (31); HR-MS: *m/z* = 356.2579, calcd. for $C_{23}H_{33}NO_2^+$: 356.2584.

Acknowledgements

This work was supported by DGICYT, Spain (project BQU-CTQ2012-30930), and Generalitat de Catalunya (project 2009 SGR 1024). Dr. Albert Palomer (Grupo Ferrer, Barcelona) is thanked for generous support.

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