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Boron-Based Dipolar Multicomponent Reactions: Simple Generation of Substituted Aziridines, Oxazolidines and Pyrrolidines

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In memory of Gerhard Hesse

Abstract: New multicomponent reactions of aldehydes, isocyanides, trialkylboron reagents and dipolarophiles have been developed as an efficient route to diverse scaffolds, including aziridines, oxazolidines and poly-substituted pyrrolidines. This chemistry, inspired by a report by Hesse in 1965, is simple and involves mild conditions. Computational studies provide a basis to investigate the stereochemical features observed in the formation of oxazolidines and four-component adducts, and permit identification of potential factors that might influence the outcome of the multicomponent reaction. Thus, a rational screening of all the components and reaction parameters is made to examine the manifold mechanistic pathways and establish the practical limits for standard applications. Finally, intramolecular and solid-supported versions of these reactions bring new synthetic possibilities and practical protocols. Overall, the results describe a new family of multicomponent reactions valuable not only for organic reactivity, but also for combinatorial chemistry and drug discovery.

Keywords: boranes · cycloaddition · heterocycles · isocyanides · multicomponent reactions

Introduction

Multicomponent reactions (MCRs) are domino processes in which three or more reactants interact to form an adduct in a single operation. MCRs constitute a fast-growing field of enormous importance in organic chemistry[1] as they embody many features of the ideal synthesis, such as atom and step economy, convergence and structural diversity.[2] Progress in this area has allowed the use of this methodology in target-oriented synthesis, parallelisation protocols and diversity-oriented synthesis, thus enabling the preparation of natural products and bioactive compounds.

Isocyanides are arguably the most prolific functional group for MCRs.[3] In recent times new and exciting results have brought great attention to this field.[4] In pursuing the development of new MCRs,[5] we considered the interaction of electrophilic boron reagents with isocyanides as the initial step to generate reactive intermediates amenable to further reactivity.[6] A literature search revealed a fascinating process described by Hesse and co-workers in 1965, which involves the generation of oxazolidines in useful yields from the interaction of alkylboranes, aldehydes and isocyanides.[7] The authors pointed out the intermediacy of an azomethine ylide, which may undergo a dipolar [3+2] cycloaddition with a second equivalent of the aldehyde to furnish the final adduct in a stereoselective manner (Scheme 1). Surprisingly, almost no references to this work have been reported.[8] The process, the keystone of which is the reaction between the isocyanide and the borane,[9] can be reshaped and, through different trappings of the dipolar intermediate, can provide a variety of scaffolds, thus exploiting the rich chemistry of azomethine ylides.[10,11]

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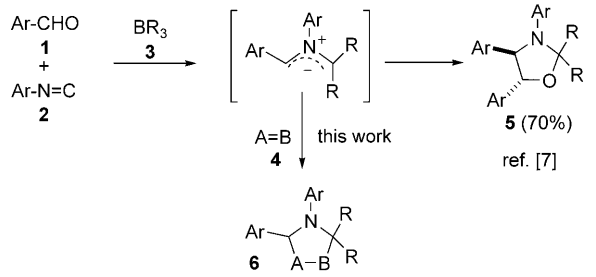


Scheme 1. Generation of five-membered N-heterocycles from the interaction of isocyanides, aldehydes, alkylboranes and dipolarophiles through azomethine ylides.

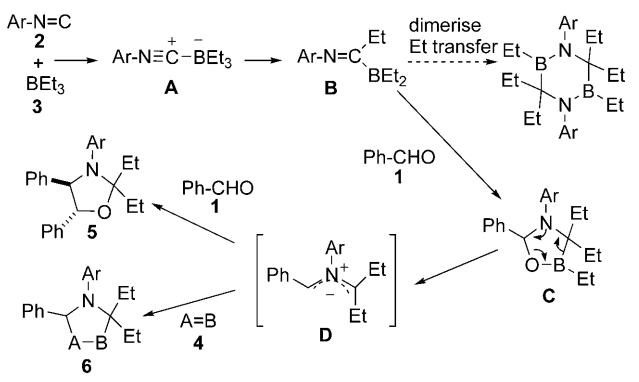
Herein, we report a new set of MCRs involving aldehydes, isocyanides, trialkylboron reagents and dipolarophiles that is well suited to affording a variety of scaffolds comprising aziridines, oxazolidines and poly-substituted pyrrolidines. We used computational studies to unravel the mechanistic details of the stereochemical preferences of the processes. Lastly, we established the scope and limitations of the new MCRs, and also devised intramolecular and solid-supported versions of these reactions.

Results and Discussion

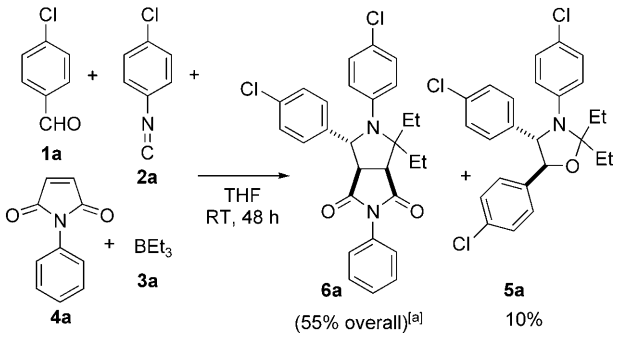
Mechanistic proposal: The suitability of the MCR involving the interaction of four reactants (aldehydes, isocyanides, trialkylboranes and dipolarophiles) to become a productive process depends on three critical factors: firstly, the feasibility of the domino process that links the four chemical inputs to yield the desired cycloaddition;[12] secondly, the generality of the process, which is mainly determined by the range of reactivity for each component; and lastly, the reaction parameters required for achieving useful transformations under mild conditions. These issues are particularly challenging due to the number and nature of the reactive species presumably engaged in the mechanism, and the manifold evolutionary pathways they may follow. Thus, as illustrated in Scheme 2, the process could start with the formation of an initial adduct **A** arising from the addition of isocyanide **2** to borane **3**, which after alkyl migration would yield an iminoborane **B**, which could dimerise and then either undergo a second ethyl migration[9] or, in the presence of aldehyde **1**, could form an oxazaborolidine intermediate (**C**) en route to the azomethine ylide **D**. Finally, this dipole could efficiently trap a second equivalent of the aldehyde to yield the oxazolidine **5**. Nevertheless, the remarkable bond-forming efficiency[1c] of the MCR could be improved if it allowed incorporation of the dipolarophile species **4**, which would lead to the highly substituted pyrrolidine derivatives **6**, representing the formation of one C–N and four C–C bonds in a single event.[13]

The main feature of the process deals with a practically unexplored access route to azomethine ylides, which may tackle some synthetic niches difficult to reach through known methodologies. However, the drawbacks of the new reaction are related to the double incorporation of the alkyl groups from the borane, and the competition between the aldehyde and the dipolarophile for trapping the azomethine ylide. The oxazolidine adduct contains two different moieties from the starting aldehyde, so its formation can be regarded as a chemo-differentiating reaction, a burgeoning family of processes with great synthetic potential.[14] Moreover, the new MCRs are susceptible to many side reactions, such as the aforementioned (and undesired) formation of the isocyanide–borane complexes,[9] the interaction of the isocyanide with the dipolarophile,[3c,15] and Passerini-type reactions promoted by the Lewis acidity of the borane.[16]

As proof of concept, we reacted an equimolecular mixture of *p*-chlorobenzaldehyde (**1a**), *p*-chlorophenyl isocyanide (**2a**), triethylborane (**3a**) and *N*-phenylmaleimide (**4a**) in THF at room temperature, to obtain the four-component-reaction (4CR) adduct **6a** as a 4:1 mixture of two stereoisomers (the minor isomer being the *all-cis* epimer) in an overall yield of 55% together with lesser amounts (≈10%) of the corresponding *trans*-oxazolidine **5a** (Scheme 3). The relative stereochemistry of compounds **5a** and **6a** was established by NMR methods (the NOEs being of diagnostic value). Incidentally, the structural assignment for the oxazolidine derivative agrees with that reported by Hesse, which he obtained by using chemical correlation studies.[7]



Scheme 2. Mechanistic proposal.



Scheme 3. 4CR leading to pyrrolidine derivative **6a**. [a] 4:1 isomeric ratio, whereby **6a** is the major isomer and the minor isomer is the *all-cis* compound.

Computational analysis: Quantum chemistry computations were performed to gain insight into the stereochemical preferences of the chemical processes involved in these MCRs. To this end, a series of model compounds that includes methylborane, phenyl isocyanide, benzaldehyde and *N*-phenylmaleimide was considered in calculations, and the relative free energies between chemical reactants, products and transition states (TSs) were determined at the MP2/6-311G-(d,p)+[CCSD-MP2/6-31G(d)] level (see the Experimental and Computational Section).

*Formation of azomethine ylide **D***: According to the reaction mechanism (Scheme 2), the iminoborane intermediate **B**, generated after alkyl migration in the initial adduct **A**, in the presence of aldehyde **1** yields the azomethine ylide **D** via the oxazaborolidine intermediate **C**. For the model compounds considered in the present computations, formation of oxazaborolidine **C** is highly favourable (-17.9 kcal mol^{-1}), but the exothermicity of this process is counterbalanced by the energy required to open the oxazaborolidine ring to yield the azomethine ylide **D**. As a result, the ylide **D** is slightly stabilised relative to the separated reactants (intermediate **B** and benzaldehyde; see Figure 1). The orientation of the two benzene rings in **D** defines two configurations denoted here as **D**-*cis* and **D**-*trans*, which mimic the W- and S-type configurations of ylides (Figure 2). The **D**-*trans* species is marginally favoured (0.4 kcal mol^{-1}) compared to the **D**-*cis* form. Accordingly, both species can a priori participate in the reaction with either another molecule of aldehyde to yield oxazolidine **5** or with dipolarophile **4** to generate adduct **6**.

*Formation of oxazolidine **5***: The azomethine ylide **D** can react with benzaldehyde to yield oxazolidine **5**, which can exist in two stereoisomeric arrangements (*trans* and *cis*, see Scheme 3). Formation of **5** is predicted to be very favourable (around -42 kcal mol^{-1}; see Figure 1), *trans*-**5** being favoured by 2.4 kcal mol^{-1} relative to *cis*-**5**. When the [3+2] cycloaddition involves the azomethine ylide **D**-*cis*, the TS leading to *trans*-**5** is destabilised by 7.0 kcal mol^{-1} relative to the separate reactants, whereas the TS yielding *cis*-**5** is further destabilised by 2.6 kcal mol^{-1} (Figure 1). Such a difference can be attributed to two factors. First, the more eclipsed approach of the reactants in the TS *cis*-**5**, as noted in the Newman projection along the forming C–C bond (see Figure 3). Second, the larger steric repulsion due to the approach of the benzene rings in the TS *cis*-**5**, as noted in the short contact between the hydrogen atoms of the benzene rings (2.31 Å; see Figure 3). On the other hand, when the cycloaddition takes place starting from the ylide **D**-*trans*, there is an additional destabilisation (by around 2 kcal mol^{-1}) in the TSs leading to oxazolidine **5**, which reflects the increased eclipsed character of the incoming reactants (note also the short H···H contact, 2.27 Å, found in TS *trans*-**5**; see Figure 3). Overall, the results indicate that the stereoselective formation of *trans*-**5** (Scheme 3) can be attributed to the kinetic preference associated with the *trans* cycloaddition pathway originating from the reaction of benzaldehyde with the **D**-*cis* form of the azomethine ylide.

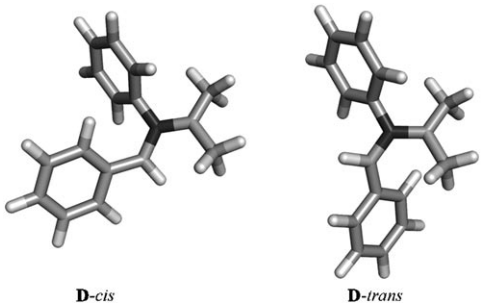


Figure 2. Representation of the *cis* and *trans* forms of the azomethine ylide **D**.

Inspection of the geometries of the most favoured TSs reveals the asynchronicity of the bond formation in the cycloaddition reaction leading to *trans*-**5** (i.e. the lengths of the forming C–C and C–O bonds are 2.15 and 2.42 Å, respectively), which is in contrast with the similar lengths (C–C:

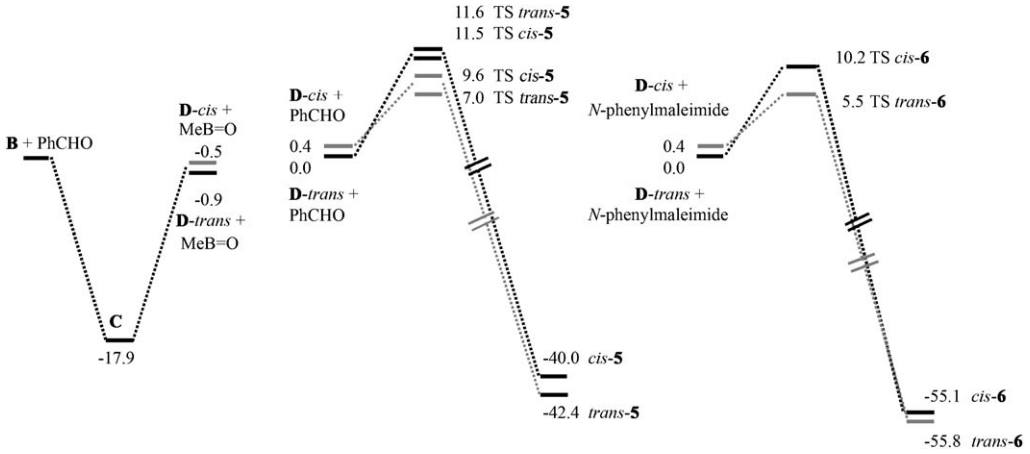


Figure 1. Diagram of the free energy differences [kcal mol^{-1}] for the chemical species involved in the formation of oxazolidine **5** and pyrrolidine **6**.

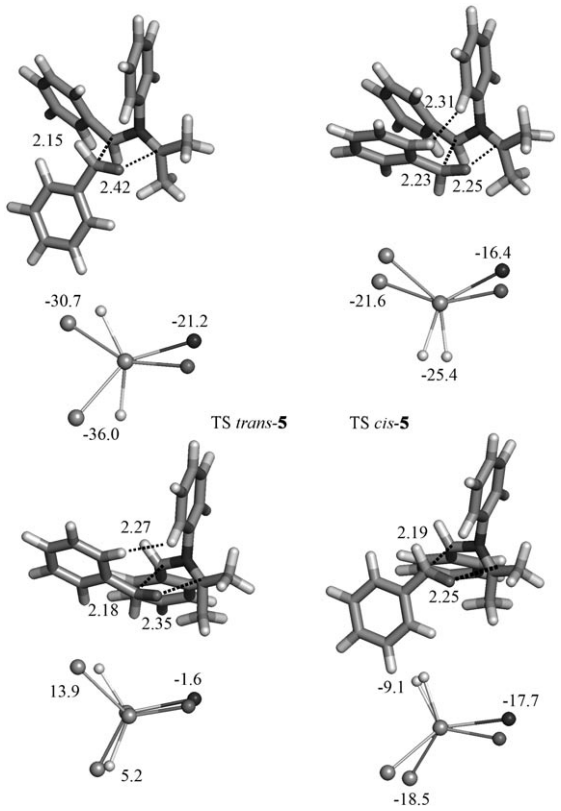


Figure 3. Representation of the TSs leading to *trans* and *cis* forms of oxazolidine **5** formed from (top) **D**-*cis* and (bottom) **D**-*trans* forms of the azomethine ylide. Newman projections viewed from along the forming C(benzaldehyde)–C(ylide) bond are also shown (distances and torsional angles are in Å and degrees, respectively).

2.23 Å; C–O: 2.25 Å) found in the TS leading to *cis*-**5**. These trends, which differ from the negligible asynchronicity found for the corresponding [3+2] cycloaddition between benzaldehyde and nitrile-containing carbon ylides reported in previous studies,[17] most likely reflect the influence of the substituents attached to the ylide **D** and the steric effects arising from the aromatic ring bound to the nitrogen atom of the ylide.

Formation of pyrrolidine ***6***: The azomethine ylide **D** may interact with *N*-phenylmaleimide to afford the desired pyrrolidine **6**, which can display two possible stereoisomeric arrangements (*trans*, *cis*) for the C-phenyl ring coming from intermediate **D** with respect to the maleimide ring, the *trans*-**6** adduct being the major component (ratio 4:1) of the mixture (see Scheme 3). The interaction between the ylide and the dipolarophile is conditioned by the presence of the bulky benzene rings, which thus only enables the approach of the reactants through a reactive pathway where the benzene rings adopt an *anti* orientation. Accordingly, the reaction of *N*-phenylmaleimide with the **D**-*cis* ylide exclusively affords *trans*-**6**, whereas reaction with **D**-*trans* yields *cis*-**6**. Computations point out that the formation of pyrrolidine **6** is highly exothermic (around 55 kcal mol^{-1}), and the pyrrolidine *trans*-**6** is predicted to be 0.7 kcal mol^{-1} more favourable than the *cis*-**6** adduct (Figure 1). Remarkably, the TS leading to *trans*-**6** is favoured by 4.7 kcal mol^{-1} compared to that associated with the formation of *cis*-**6**. In the two TSs, there is a steric contact between the *N*-phenyl ring in the ylide and the *N*-phenylmaleimide moiety (distances of 2.31 and 2.45 Å in TS *trans*-**6** and TS *cis*-**6**, respectively; see Figure 4). However, the more eclipsed approach of the reactants in TS *cis*-**6** explains the larger stability of the TS *trans*-**6**.

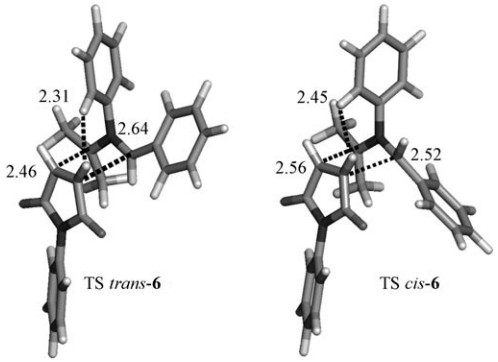


Figure 4. Representation of the TSs leading to *trans* and *cis* forms of pyrrolidine **6** (distances are in Å).

Overall, the results point out that the stereochemical preferences in the formation of oxazolidine **5** and pyrrolidine **6** are dictated by the kinetically more favoured TS, which corresponds to the one leading to *trans*-**5** and *trans*-**6**, respectively. Notably, the latter is predicted to be 1.5 kcal mol^{-1} more favourable than the former, which agrees qualitatively with the larger amount found for pyrrolidine **6** (see Scheme 3). Nevertheless, the preceding discussion also suggests that the precise outcome of the MCR may be very sensitive to the nature of the substituents attached to both isocyanide and aldehyde, the differential stabilisation played by the solvent on the [3+2] cycloaddition, and the chemical features of the dipolarophile, which might affect the relative stability of the *cis* and *trans* species of the ylide **D** and the competitive reaction of the ylide with either the aldehyde or the dipolarophile.

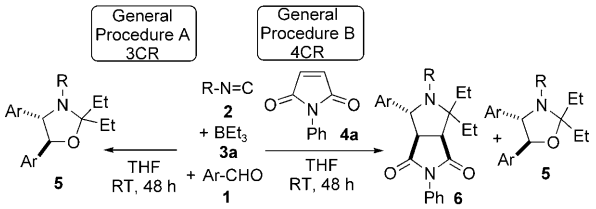
Reaction scope: Upon surveying the reaction conditions, we found that the best solvents were diethyl ether (Et_2O) and THF; no reaction occurred in toluene, dichloromethane, DMF, CH_3CN or MeOH. Surprisingly, water (50% in THF) is well tolerated and it is even possible to run the MCR in micellar systems (H_2O/sodium dodecyl sulfate). The reaction proceeds within a useful temperature range: from −20 to +20 °C. At lower temperatures, there is no noticeable reactivity, whereas at higher values, the starting materials severely decompose (the formation of isocyanide–borane adducts is presumably favoured). Therefore, all the following experiments were run at room temperature, after pre-mixing the four components at 0 °C. Microwave irradiation seems to increase the formation of oxazolidines, consequently lowering

the amount of the 4CR adduct. The use of a set of additives including Lewis acids, bases, ligands and dehydrating agents such as scandium(III) trifluoromethane sulfonate (scandium triflate, $Sc(OTf)_3$), $Mg(ClO_4)_2$, *N*,*N*-diisopropylethylamine (DIPEA), 2-chloropyridine[18] or molecular sieves (4 Å), respectively, precludes the reaction. In contrast, the chemistry proceeds normally with galvinoxyl and with limited exposure to oxygenated atmospheres (no effect on the yields and selectivity), which seems to rule out a radical process.

Isocyanide range: We determined the range of reactivity for each component by using comparable sets of reactants and reaction conditions. Starting with isocyanides **2**, we found that only the aromatic derivatives were productive under the mild conditions tested. For example, *p*-methoxyphenyl isocyanide (**2b**) was efficiently incorporated into oxazolidine **5b** and the 4CR adduct **6b** (Table 1, entries 1 and 2, respectively). As usual, we obtained epimeric mixtures (≈7:3) of the 4CR adducts, the major stereoisomers being depicted in Table 1. *p*-Tolyl (**2c**) and phenyl isocyanides (**2d**) afforded the expected adducts in somewhat lower yields (Table 1, entries 3 and 4). Halo-substituted aromatic derivatives also reacted in a convenient manner (Table 1, entries 5–7), whereas the deactivated 4-ethoxycarbonyl derivative (**2f**, Table 1, entry 8) was considerably less reactive and the 3- and 4CR adducts could only be detected in minute amounts. Cyclohexyl (**2g**), cyclohexenyl (**2h**), benzyl (**2i**) and deactivated isocyanides, such as tosylmethyl isocyanide (**2j**), were inert under the usual conditions or gave rise to complex mixtures (Table 1, entries 9–12). As revealed in Table 1, the best yields were obtained with electron-rich benzene rings, which may reflect the need for nucleophilicity at both the C-terminal atom of the isocyanide and at the N atom of intermediate **B** (Scheme 2).[19] The stability of the resulting azomethine ylide may also be important for the viability of the MCRs, as it would presumably restrict the process to the presence of aromatic rings in the dipole.

Aldehyde range: Regarding the aldehydes (Table 2), we found that aromatic derivatives afforded the best conversions in both three-component reactions (3CRs; oxazolidines **5**) and 4CRs (pyrrolidines **6**). *p*-Chlorobenzaldehyde (**1a**, Table 2, entries 1 and 2) yielded the corresponding adducts in good amounts, and methyl 4-formylbenzoate (**1b**, Table 2, entries 3 and 4) was also productive. Benzaldehyde (**1c**, Table 2, entry 5) and even the electron-rich *p*-methoxybenzaldehyde (**1d**, Table 2, entry 6) afforded the corresponding MCR adducts, although in lower yield in the latter case. Among the heteroaromatic aldehydes, furfural (**1e**, Table 2, entry 7) yielded the corresponding adduct **6g**, whereas pyridine-3-carbaldehyde (**1f**, Table 2, entry 8) gave predominantly the oxazolidine **5h** in low yield; the 4CR adduct was only detected under these conditions (general

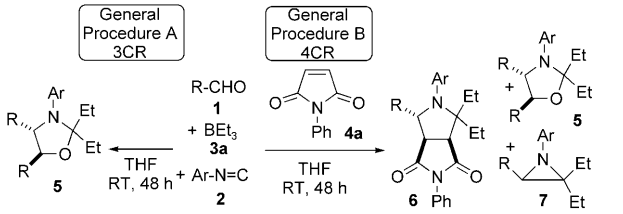
Table 1. Range of isocyanides **2**.



Entry[a]	Procedure	R	Adduct	Yield[b]
1	A	4-MeO-C_6H_4- (**2b**)	**5b**	85
2	B	4-MeO-C_6H_4- (**2b**)	**6b**[c]	68
3	A	4-Me-C_6H_5- (**2c**)	**5c**	67
4[d]	A	C_6H_5- (**2d**)	**5d**	22
5	A	4-Cl-C_6H_4- (**2a**)	**5a**	65
6[e]	B	4-Cl-C_6H_4- (**2a**)	**6a**	55
7	A	4-F-C_6H_4- (**2e**)	**5e**	36
8[f]	B	4-EtO_2C-C_6H_4- (**2f**)	**5f/6c**	traces
9	A	cyclohexyl- (**2g**)	–	–
10	A/B	1-cyclohexenyl- (**2h**)	–	–
11	A	benzyl- (**2i**)	–	–
12	A	tosylmethyl- (**2j**)	–	–

[a] The reactions were performed following the standard procedure A or B to form respectively **5** or **6** with *p*-chlorobenzaldehyde **1a** as the aromatic aldehyde input. [b] Overall yield of isolated product. [c] Adducts **6** were generated as ≈7:3 diastereomeric mixtures, from which the major epimer was isolated and characterised. The major epimer corresponds to the depicted relative stereochemistry. [d] The reaction was performed with BBu_3 (**3b**). [e] In this experiment, oxazolidine **5a** was also generated (10%). [f] This experiment was attempted with methyl-4-formylbenzoate **1b** as the aldehyde component.

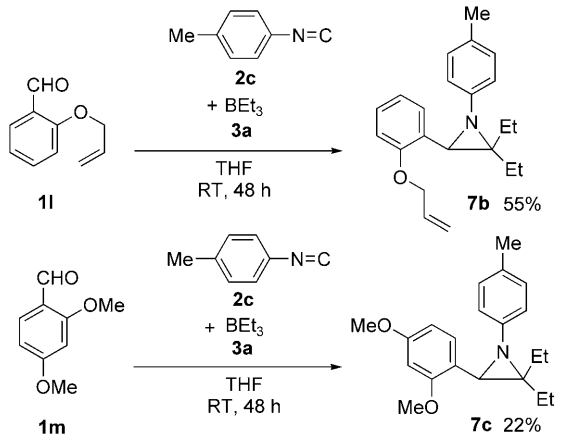
Table 2. Range of aldehydes **1**.



Entry[a]	Procedure	R	Adduct	Yield[b]
1	A	4-Cl-C_6H_4- (**1a**)	**5b**	85
2	B	4-Cl-C_6H_4- (**1a**)	**6b**[c]	68
3	A	4-MeO_2C-C_6H_4- (**1b**)	**5g**	50
4	B	4-MeO_2C-C_6H_4- (**1b**)	**6d**	24
5	B	C_6H_5- (**6e**)	**6e**	55
6[d,e]	B	4-MeO-C_6H_4- (**1d**)	**6f/7a**	25/4
7[d]	B	2-furyl- (**1e**)	**6g**	20
8[d]	A	3-pyridyl- (**1f**)	**5h**	62[f]
9	B	CH_2=CH- (**1g**)	**6h**	40
10[d]	B	Ph-CH=CH- (**1h**)	**6i**[g]	71
11	B	C_5H_{11}-C≡C- (**1i**)	**6j**	63
12	A/B	$(Me)_3C$- (**1j**)	–	–
13	A	EtO_2C- (**1k**)	**5i**	7

[a] The reactions were performed following the standard procedure A or B to form respectively **5** or **6**; *p*-methoxyisocyanide (**2b**) was used as the aromatic isocyanide input if not stated otherwise. [b] Overall yield of isolated product. [c] Adducts **6** were generated as ≈7:3 diastereomeric mixtures, from which the major epimer was isolated and characterised. The major epimer correspond to the depicted relative stereochemistry. [d] *p*-Chlorophenyl isocyanide (**2a**) was used as the aromatic isocyanide input. [e] Aziridine **7a** was also isolated in this experiment. [f] Following procedure B, the expected 4CR adduct was detected in minute amounts, whereas the oxazolidine **5h** adduct was obtained in 15% yield. [g] Obtained as a 7:3 mixture of stereoisomers, from which the minor adduct was isolated and characterised.

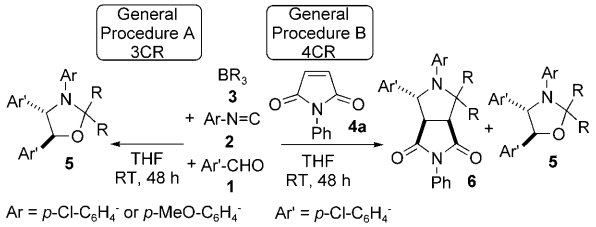
procedure B). However, this oxazolidine was conveniently generated (62%) when the 3CR protocol (general procedure A) was used, which probably means that this electrophilic aldehyde overrides maleimide as the dipolarophile input, thereby preventing the 4CR process. Interestingly, formyl groups linked to non-aromatic sp^2- or sp-hybridised carbon atoms were also reactive. Thus, acrolein (**1g**), cinnamaldehyde (**1h**) and oct-2-ynal (**1i**) readily afforded the expected MCR adducts (Table 2, entries 9–11).[20] In contrast, pivalaldehyde (**1j**) was not reactive (Table 2, entry 12) and ethyl glyoxylate (**1k**) gave low yields of the corresponding oxazolidine (**5i**, Table 2, entry 13). These results clearly indicate that electron-withdrawing substituents in aromatic rings seem to favour the MCRs, by rendering the carbonyl group more electrophilic and stabilising the anionic site in the dipole. Interestingly, strong electron-donor substituents, such as the *p*-MeO group, also provided the 4CR adduct albeit in lower yields. In this experiment the aziridine **7a** (Table 2, entry 6) was also isolated whereas the corresponding oxazolidine was not detected, probably due to the low reactivity of this aldehyde as dipolarophile in [3+2] cycloadditions. Confirming this result, the 2-allyloxy derivative **1l** and 2,4-dimethoxybenzaldehyde (**1m**) afforded aziridines **7b** and **7c**, respectively (Scheme 4), most likely by electrocyclisation of the azomethine ylide intermediate.[21,22] Overall, the reactivity pattern of aldehydes seems to parallel that of the carbonyl precursors of the azomethine ylides generated by conventional methods (e.g. condensation, decarboxylation, prototropy, carbene insertion); the aromatic derivatives are the most widely used for preparative purposes.[10]



Scheme 4. Aziridine formation from *o*-alkoxybenzaldehydes.

Boron reagent range: The borane component is the main limitation in this MCR: we only found acceptable reactivity by using the commercially available ethyl (**3a**) and butyl (**3b**) boranes (Table 3, entries 1 and 2). However, borane itself afforded minute amounts of the expected adduct (as a somewhat unstable compound), together with the benzylic alcohol from the reduction of the aldehyde (Table 3, entry 3).[23] Triphenyl boron (**3d**),[24] 9-benzyl-BBN (**3e**; 9-BBN: 9-borabicyclo[3.3.1]nonane) and $BF_3{\cdot}Et_2O$ (**3f**) led to complex mixtures (Table 3, entries 4–6). Whether these MCRs can be improved with more suitable reaction conditions, namely by minimising unproductive side reactions, remains to be determined.

Table 3. Set of boron reagents.

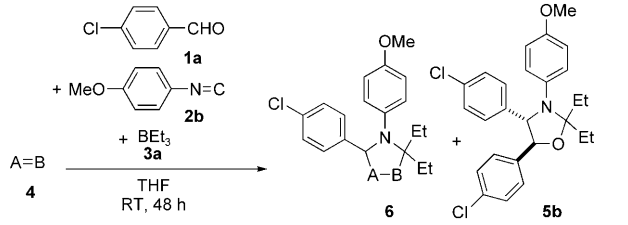


Entry[a]	Procedure	R	Adduct	Yield[b]
1	A	Et (**3a**)	**5a**	65
2	A	Bu (**3b**)	**5j**	40
3[c]	B	H (**3c**)	**6k**[d]	3
4	B	C_6H_5- (**3d**)	–	–
5	B	9-benzyl-BBN (**3e**)	–	–
6	B	F (**3f**)	–	–

[a] The reactions were performed following the standard procedures A or B to form respectively adducts **5** or **6** with *p*-chlorobenzaldehyde as the aromatic aldehyde input and *p*-chlorophenyl isocyanide as the isocyanide input if not stated otherwise. [b] Overall yield of isolated product. [c] *p*-Methoxyphenyl isocyanide was used in this experiment. [d] Adduct **6k** was generated as a ≈4:1 diastereomeric mixture.

Dipolarophile range: Regarding the dipolarophile **4** (Table 4), we obtained the highest yields of the 4CR adducts using *N*-phenylmaleimide (**4a**, Table 4, entry 1), which is the reference compound in many dipolar cycloadditions. It should be noted that azomethine ylides preferentially react with electron-deficient dipolarophiles.[25] As such, dimethyl acetylenedicarboxylate (**4b**, Table 4, entry 2), dimethyl fumarate (**4c**, Table 4, entry 3) and fumaronitrile (**4d**, Table 4, entry 4) were found to be reactive in our system. The 4CR adducts were isolated (although the adduct from acetylene dicarboxylate was somewhat unstable), and in all applicable cases the stereochemistry of the dipolarophile was conserved (7:3 mixtures of isomers in Table 4, entries 1, 3 and 4). Methyl acrylate (**4f**, Table 4, entry 5) afforded the 4CR adduct **6o** (24%, Figure 5) together with oxazolidine **5b** as the major compound (76%). The structure of **6o** was unambiguously assigned by diagnostic correlations from NMR experiments (^1H, ^{13}C, COSY, HSQC, HMBC, NOESY). In this case, the non-symmetrically substituted dipolarophile behaves in a particular manner, as it not only affords a *cis* stereochemistry, but seemingly alters the regiochemistry (taking into account the expected polarity in this type of process). Literature precedents on cycloadditions involving acrylates and azomethine ylide intermediates generally report low selectivity profiles, and in most cases the predominant regiochemistry is opposite to that observed in our system.[26] Diethyl azodicarboxylate (**4e**, Table 4, entry 6) also reacted conveniently but again the slight instability of the adduct prevented its full characterisation. The assay

Table 4. Set of dipolarophile reagents **4**.



Entry	A=B	Adduct	Yield[a]
1	*N*-phenylmaleimide (**4a**)	**6b**[b]	85
2	MeO_2C-C≡C-CO_2Me (**4b**)	**6l**[b]	49[c]
3	dimethyl fumarate (**4c**)	**6m**[d]	26
4	fumaronitrile (**4d**)	**6n**[b]	20[e]
5	methyl acrylate (**4f**)	**6o/5a**	24/76
6	EtO_2C-N=N-CO_2Et (**4e**)	**6p**	34
7	1,4-naphthoquinone (**4g**)	–	traces
8	ethyl 3-coumarincarboxylate (**4h**)	**5b**	58
9	diethyl benzylidenemalonate (**4i**)	**5b**	35
10[f]	norbornene (**4j**)	–	–
11[f]	2,3-dihydrofuran (**4k**)	–	–

[a] Overall yield of isolated product. [b] Adducts **6** were generated as ≈7:3 diastereomeric mixtures, from which the major epimer was isolated and characterised. The major epimer corresponds to the depicted relative stereochemistry. [c] Unreacted aldehyde was recovered (50%). [d] Obtained as an inseparable 6:4 mixture of stereoisomers. [e] Unreacted aldehyde was recovered (78%). [f] In these entries, 4-ethoxycarbonylphenyl isocyanide (**2f**) and methyl 4-formylbenzoate (**1b**) were used as the isocyanide and aldehyde components, respectively.

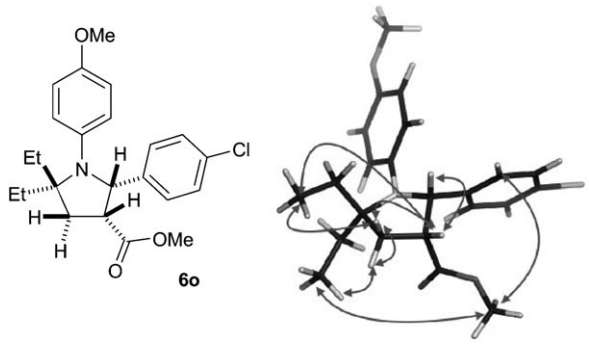
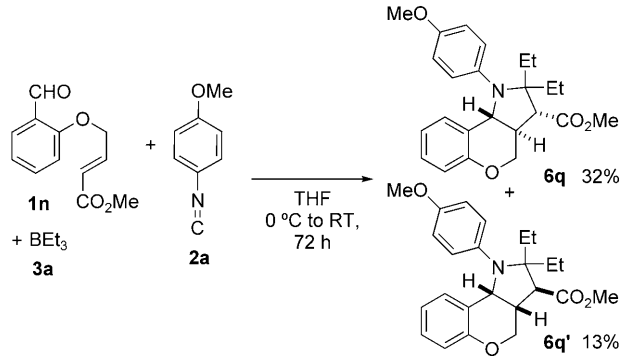


Figure 5. 4CR adduct **6o**. Diagnostic correlations in the NOESY spectrum.

with 1,4-naphthoquinone (**4g**, Table 4, entry 7) afforded a complex mixture in which the expected adduct together with its oxidation product were each detected in minute amounts.

On the other hand, when more sterically hindered dipolarophiles, such as ethyl 3-coumarincarboxylate (**4h**, Table 4, entry 8) and diethyl benzylidenemalonate (**4i**, Table 4, entry 9) were used, the oxazolidine **5b** was the only isolated product. Two examples of inverse electron-demanding cycloaddition were attempted by using non-activated (electron-rich) dipolarophiles, namely norbornene (**4j**, Table 4, entry 10) and 2,3-dihydrofuran (**4k**, Table 4, entry 11).[25] In both cases, to adjust the polarity of the process, 4-ethoxycarbonylphenyl isocyanide (**2f**) and methyl 4-formylbenzoate (**1b**) were used as reaction partners. However, no productive reaction was detected under the mild conditions used, and only the corresponding oxazolidines were formed. As noted above, the complexity of the mechanism promotes competition between two species (the aldehyde and the nominal dipolarophile) for trapping the dipole, which limits the use of the less reactive dipolarophiles. Moreover, the need to perform the processes at room temperature (cycloadditions with azomethine ylides are typically conducted at much higher temperatures) to avoid side reactions diminishes the feasibility of some combinations, particularly those involving the less reactive species.

Intramolecular MCRs: We also explored the possibility of promoting intramolecular MCRs by taking advantage of the structural diversity provided by this methodology and the extraordinary success recently achieved in this field.[10c,f,27] Again, the mild conditions demanded use of electron-deficient olefin moieties (for instance, the deactivated *o*-allyloxybenzaldehyde (**1l**) failed to give any pyrrolidine adduct, and afforded the aziridine **7b** instead; see Scheme 4). Hence, aldehyde **1n**[28] was chosen as an alternative substrate (Scheme 5). Rewardingly, the MCR yielded the chromenopyrrolidine adducts (**6q** and **6q′**) in an overall yield of 45%, as a 2:1 mixture of stereoisomers displaying *trans* and *cis* ring fusions, respectively.



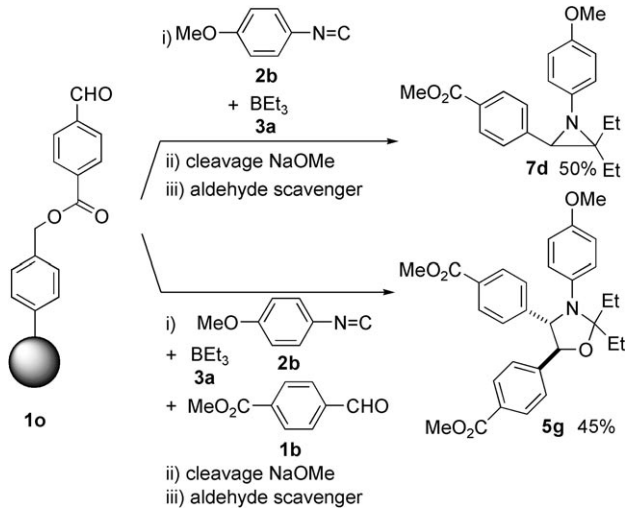
Scheme 5. Intramolecular MCR.

Recent precedents to access these heterocyclic systems used different methodologies to generate the azomethine ylide.[29] However, the method presented here seems to be the most straightforward for the introduction of two alkyl substituents at position 2 of the tricyclic scaffold.[30]

Solid-supported MCRs: Many side reactions do take place in these MCR processes and the undesired by-products, together with remaining starting materials (usually aldehyde and dipolarophile), can produce very complex mixtures, as noted in the HPLC profile of the crude organic extract from the experiment leading to **6f** (see the Supporting Information). Therefore, the purification of the expected adducts is extremely challenging, especially in cases with low yields. Solid-phase versions of MCRs[31] might be a practical and ef-

ficient way to facilitate removal of undesired products and minimise the impact of side reactions. For instance, supporting the aldehyde component on a resin would secure its role as the azomethine ylide precursor, and would prevent it from acting as a dipolarophile. Remarkable work in the area has shown the possibility of conducting dipolar cycloadditions in the solid phase.[32] Hence, we decided to link the aldehyde to a suitable resin, generate the azomethine ylide and quench the reaction in situ with the dipolarophile, or promote the selective formation of the aziridine and oxazolidine systems. In this way, only the desired products would remain attached to the resin, ideally to furnish pure samples after the cleavage. Also, it is conceivable to generate the linked dipolar intermediate, to elute all other compounds and, in a sequential manner, promote the cycloaddition step without interferences.

To explore these possibilities, we first linked 4-formylbenzoic acid to hydroxymethyl polystyrene resin, and afterwards we added the borane **3a** and isocyanide **2b** and stirred the resin at room temperature (Scheme 6). After



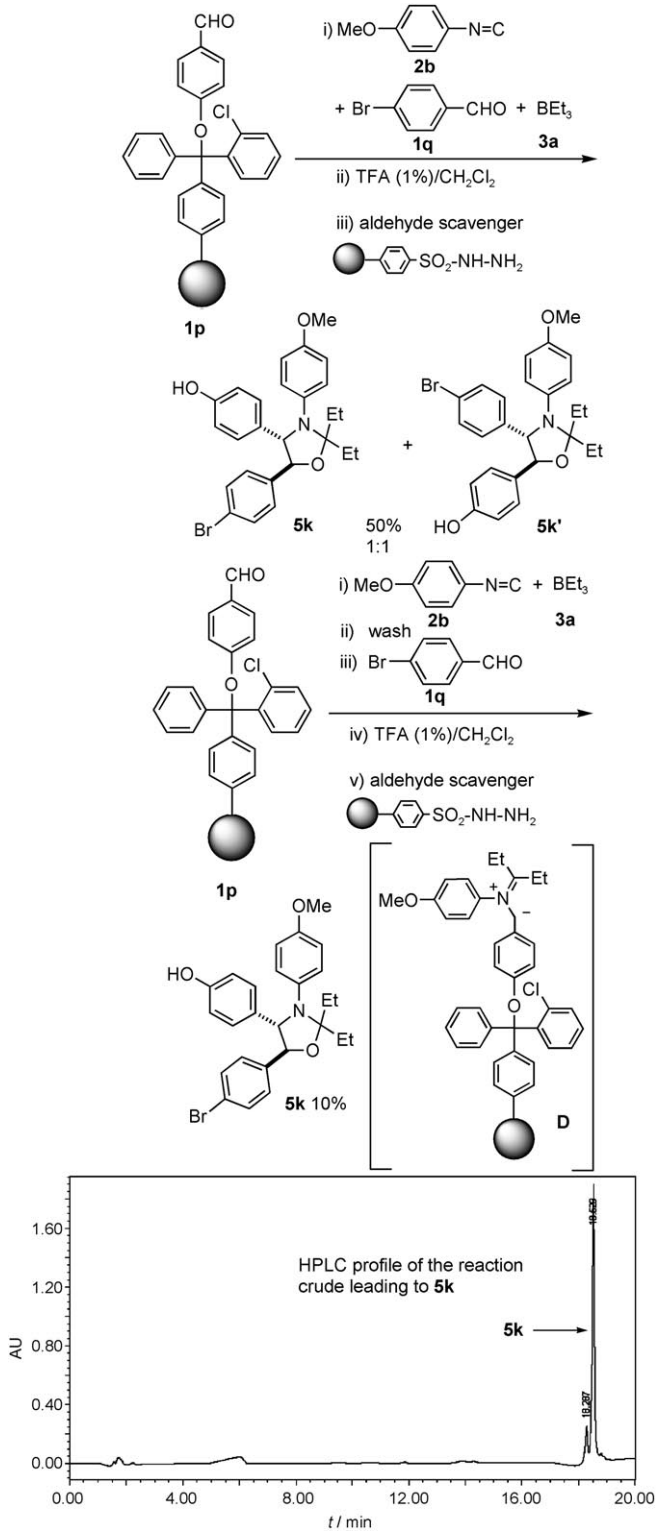
Scheme 6. Solid-supported versions of the MCRs.

standard washings and a mild sodium methoxide cleavage, the corresponding aziridine **7d** was obtained in 50% yield. Remarkably, this compound cannot be formed in solution, as the aldehyde efficiently traps the dipole once generated, which leads to the corresponding oxazolidine **5g**. In another experiment, we specifically promoted the latter reaction, which took place smoothly upon interaction with the aldehyde component **1b**. The resulting product was identical in all aspects to that previously obtained in the solution phase. The yields were calculated upon the loading of the aldehyde onto the resin. In spite of using excesses of the non-supported components, we could not accomplish quantitative transformations, which probably reflects some practical limitations in reaching sterically crowded regions in the solid support. However, the use of a solid-supported scavenger[33] efficiently removes the unreacted aldehyde, and affords the pure MCR adducts.

We then promoted the formation of "mixed oxazolidines" in a 4CR using two different aldehydes. A solution-phase approach would be unproductive, because at least four compounds would be generated (two from homo-combinations plus two from hetero-couplings). In an initial assay, we first linked 4-hydroxybenzaldehyde to a 2-chlorotrityl chloride resin, and then reacted it with borane **3a**, *p*-bromobenzaldehyde (**1q**) and isocyanide **2b**.

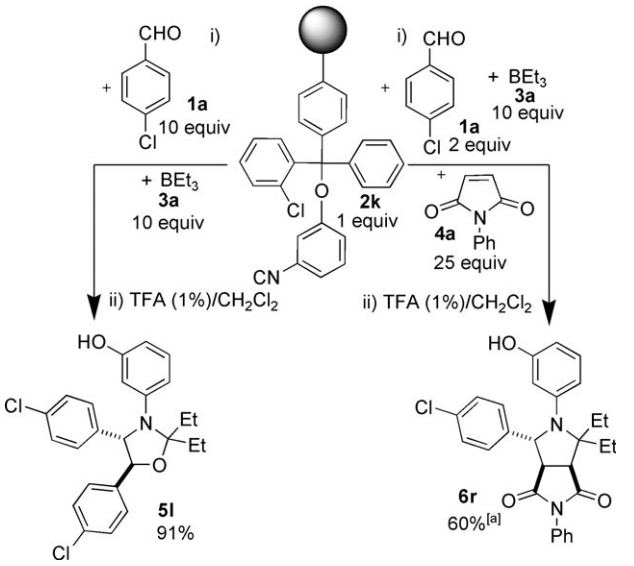
After the usual sequence of elutions, cleavage and a final treatment with a solid-supported aldehyde scavenger, we obtained a nearly equimolecular mixture of the two hetero-coupled oxazolidines **5k** and **5k′** which were not separated (Scheme 7). This suggested that two azomethine ylides had been generated: one from the aldehyde in solution, trapped by the linked aldehyde, and vice versa. To solve this problem, we performed the reaction in a sequential manner, and the protocol was modified to include washings after the generation of the linked dipole **D**, then we added the solution of aldehyde **1q**, and let the reaction proceed (Scheme 7). In this way, we managed to selectively prepare the mixed oxazolidine **5k** (10%, unoptimised). The low yield may be attributable to the manipulation of the azomethine ylide. Remarkably, this methodology allows the selective generation of solid-supported azomethine ylides and their interactions with dipolarophiles in a sequential manner. The high purity of the crude reaction mixture obtained in this experiment compared to that obtained with previous solution-phase processes is noteworthy (see the Supporting Information). Interestingly, this approach distinguishes between two pseudo-equivalent partners in chemo-differentiating ABB′-type processes, and consequently can significantly improve the synthetic applications of these useful procedures.[14,34]

A first attempt to perform a 4CR using the solid-supported aldehyde **1o** (Scheme 6), *p*-methoxyphenyl isocyanide (**2b**), *N*-phenylmaleimide (**4a**) and triethylborane (**3a**) afforded a complex mixture, probably due to the degradation of the desired adduct during the cleavage with sodium methoxide (based on mass spectrometry evidence). We then attempted the same reaction with the aldehyde-loaded resin **1p** (Scheme 7) and, although we did detect the expected 4CR adduct, the overall yield was very low. We then decided to use a solid-supported isocyanide[35] to avoid the dimerisation process of the intermediate **B** (see Scheme 2). The 2-chlorotrityl resin was loaded with *N*-(3-hydroxyphenyl)formamide and the resulting polymer was subjected to dehydration by using the Hulme protocol, to yield the solid-supported isocyanide **2k**.[35a] The loading of the solid-supported formamide was then evaluated with a TFA cleavage protocol. In a parallel experiment, the cleavage of the solid-supported isocyanide **2k** afforded the same starting formamide. Thus, we roughly estimated the loading of **2k** to be about 0.4 mmol g^{-1}, which suggests that the isocyanide or the formamide is partially cleaved during the dehydration process. A mixture of this isocyanide-functionalised resin and *p*-chlorobenzaldehyde (**1a**) was added to a solution of triethyl-



Scheme 7. Solid-phase approaches to mixed oxazolidines. TFA: trifluoroacetic acid.

borane in THF and stirred for 48 h (Scheme 8). After cleavage with 1% TFA–dichloromethane, the pure oxazolidine **5l** was obtained in 91% yield. In another experiment, the solid-supported isocyanide **2k** was reacted with triethylborane (**3a**), *p*-chlorobenzaldehyde (**1a**) and *N*-phenylmaleimide (**4a**) in a 4CR; standard TFA cleavage afforded the expected adduct **6r** (60%) in a stereoselective manner.[36] Thus, we have conducted all our new MCRs in the solid phase, thereby showing the feasibility of this strategy to facilitate access to pure compounds.



Scheme 8. MCRs using solid-supported isocyanide. [a] 4:1 isomeric ratio, whereby **6r** is the major isomer and the minor isomer is the *all-cis* compound.

Conclusion

Based on an initial report by Hesse and co-workers, we have designed and implemented a family of MCRs involving the interaction of isocyanides, aldehydes, boranes and dipolarophiles to yield pyrrolidine, aziridine and oxazolidine adducts in a single step, with high atom economy and bond-forming efficiency. These scaffolds have relevant presence in bioactive compounds. Moreover, oxazolidines are also found in pro-drugs as protected forms of 1,2-aminoalcohols.[37] Incidentally, this approach can also stereoselectively furnish these compounds after the customary hydrolysis of the oxazolidine precursors. Calculations performed for model compounds indicate that the stereochemical preferences in the reaction outcome are dictated by the TSs that are more favoured kinetically, which correspond to those leading to *trans* stereochemistries in the cycloaddition of the azomethine ylide **D**-*cis* with either the aldehyde or dipolarophile. However, these studies also show that the precise evolution of the MCRs may be subtly modulated by factors such as the nature of the substituents attached to both the isocyanide and the aldehyde units, or the chemical features of the dipolarophile. This has allowed a rationalisation of the manifold mechanistic pathways and established the practical limits for standard reactions. Furthermore, intramolecular and solid-supported versions of these processes have been developed

and, in the latter cases, the controlled environment achieved using linked substrates allows selective reactions, and facilitates purification. Our future work will follow along these lines, namely, to increase the reactivity range of some components (particularly the boranes)[38] and to expand the synthetic usefulness and scaffold variability for this complex family of MCRs.

Experimental and Computational Section

General procedure A: A solution of isocyanide (1 mmol, 1 equiv) and aldehyde (2 mmol, 1 equiv) in THF (2 mL) was added slowly to a solution of trialkylborane in THF (1 M, 1.2 mmol, 1.2 equiv) at 0 °C. After 3 min of stirring at this temperature, the ice bath was removed and the reaction mixture was stirred for 48 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 **5**.

General procedure B: A solution of isocyanide (1 mmol, 1 equiv) and aldehyde (1 mmol, 1 equiv) in THF (2 mL) was added slowly to a solution of trialkylborane in THF (1 M, 1.2 mmol, 1.2 equiv) at −10 °C. Subsequently the dipolarophile was added to the mixture. After 3 min of stirring at this temperature, the cooling bath was removed and the reaction was stirred for 48 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 C: For the synthesis of aziridines in the solution phase, the stoichiometry of general procedure A was modified (aldehyde, 1 mmol, 1 equiv). After chromatographic purification, the corresponding aziridine **7** was obtained.

General procedure D (solid-phase approach, supported aldehyde): A solution of isocyanide (1.39 mmol, 8 equiv) and aldehyde (8 equiv) in THF (3 mL) was added to the solid-supported aldehyde (200 mg, loading 0.82 mmol g^{-1}, 174 μmol). The resulting suspension was added to a borane solution in THF (1 M, 3.48 mmol, 20 equiv) in a falcon tube at 0 °C. The bath was removed and the reaction mixture was stirred for 48 h at room temperature. The mixture was then transferred to a solid-phase syringe, and washed with dichloromethane (3×5 mL). The cleavage was made depending on the nature of the resin. The unreacted aldehyde was scavenged with a suspension of *p*-toluenesulfonylhydrazide polymer-bound in dichloromethane. In this way, oxazolidines **5** and aziridines **7** (without adding the aldehyde in solution) were obtained.

General procedure E (solid-phase approach, supported isocyanide): A solution of aldehyde (1.39 mmol, 17 equiv) in THF (3 mL) was added to the solid-supported isocyanide (200 mg, 3-isocyanophenylether 2-chlorotrityl polymer-bound, loading 0.4 mmol g^{-1}, 80 μmol). The resulting suspension was added to a borane solution in THF (1 M, 3.48 mmol, 20 equiv) in a falcon tube at 0 °C. The bath was removed and the reaction mixture was stirred for 48 h at room temperature. The mixture was then transferred to a solid-phase syringe, and washed with dichloromethane (3×5 mL). The cleavage was made through cleavage procedure B (see below). In this way, oxazolidines **5** and the four-component adducts **6** (adding the corresponding dipolarophile, 25 equiv) were obtained.

Cleavage A: Hydroxymethyl polystyrene resin: The resin-bound product was suspended in THF (2 mL). A solution of NaOMe in MeOH (0.5 M, 1 mmol, 5.7 equiv) was then added and the reaction mixture was stirred for 24 h. Afterwards, the solid was removed by filtration washing with dichloromethane (2 mL). H_2O (2 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.

Cleavage B: 2-Chlorotrityl polystyrene resin: The resin-bound product was treated with TFA (1 %) in dichloromethane (5×3 mL×1 min). The mixture was dropped directly onto an extraction funnel with an aqueous saturated $NaHCO_3$ solution (10 mL). After extraction with dichloromethane (3×10 mL), the combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure.

Computational studies: Full geometry optimisations were performed with the B3LYP[39] functional and the 6-31G(d)[40] basis set. The nature of the stationary points was verified by inspection of vibrational frequencies within the harmonic oscillator approximation. Intrinsic reaction coordinate calculations were carried out to check the connection between TSs and minimum-energy structures.[41] Single-point calculations were carried out at the MP2/6-311G(d,p)[42] level to determine the relative energies. Higher-order electron correlation effects were estimated from coupled-cluster singles and doubles (CCSD) calculations with the 6-31G(d) basis set. The final estimate of the electronic energies was determined by combining the MP2/aug-cc-pVDZ energy with the difference between the energies calculated at both CCSD and MP2 levels with the 6-31G(d) basis (denoted in the text as MP2/6-311G(d,p)+[(CCSD-MP2)/6-31G(d)]. Finally, zero-point, thermal and entropic corrections evaluated within the framework of harmonic oscillator rigid-rotor models at 1 atm and 298 K using the B3LYP/6-31G(d) vibrational frequencies (scaled by a factor of 0.96)[43] were added to estimate the free energy differences in the gas phase. Calculations were performed with Gaussian 03.[44]

Acknowledgements

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