malonate complex **6b**. Complex **7** did form the corresponding 2-aryl 1,3-diketone during this thermolysis, but in only 22% yield.

One would expect that rearrangement of the η^2-O,O-bound complexes to their C-bound tautomers would precede reductive elimination. Indeed, complexes of 1,3-dicarbonyl anions that we could not observe as a C-bound isomer did not undergo reductive elimination in high yield. For example, arylmalonate anions **2c** and **6c**, and acetylacetonate **7** produced Pd^0 complexes and free malonate or acetylacetone upon addition of the chelating ligands dppe, dppbz = 1,2-bis(diphenylphospnanyl)benzene (dppbz), 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (binap), and 1,1′-bis(diphenylphosphanyl)ferrocene (dppf). No complex of a C-bound anion was detected.

In summary, the greater steric hindrance of $FcPtBu_2$ (**4**), relative to that of phenylphosphanes, induces reductive elimination from complexes of typically unreactive ligands derived from malonate and actylacetonate anions. This steric effect overrides the stabilizing effect of the η^2-O,O-coordination mode and the electron-withdrawing groups on the central carbon atom of the malonate anion. Studies on the mechanism of these new reductive eliminations and the synthesis of complexes with related stabilized anions are in progress.

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A Five-Component Synthesis of Hexasubstituted Benzene**

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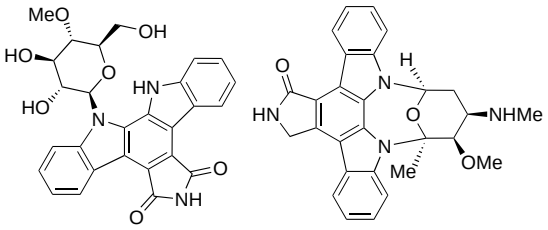
Bis(indolyl)maleimides and indolo[2,3-*a*]carbazole alkaloids constitute a rapidly growing family of natural products with diverse biological activities.[1] Thus, rebeccamycin (**1**)[2] and staurosporine (**2**)[3] are potent topoisomerase I and



1 **2**

protein kinase C inhibitors, respectively. Structurally, this class of compounds is characterized by an hexasubstituted benzene ring with a fused indolo (forming an indolocarbazole entity) and a fused lactam or an imide ring with a pendant sugar moiety. The novelty of the structures combined with their interesting biological profile have stimulated numerous synthetic efforts from both academic and industrial researchers.[4]

Transition-metal-mediated cyclization of appropriately functionalized enynes[5] and Diels–Alder cycloaddition of furan[6] are two main strategies used for the synthesis of hexasubstituted benzenes.[7] Although high level of structural complexity can be generated from these two key transformations, the overall efficiency is often counter-balanced by efforts associated with the synthesis of linear precursors. In connection with our continued interest in the development of highly efficient synthesis of druglike polyheterocycles,[8] we report herein a conceptually new strategy for the synthesis of hexasubstituted benzenes **3** based on a novel one-pot five-component domino process.[9,10]

The underlying principle of our synthesis is shown in Scheme 1. A recently developed three-component reaction based on Ugi chemistry pioneered by Ugi and co-workers[9] provides the 5-aminooxazole **7**.[11] Reaction of the latter with acyl chloride **8** (X = Cl) should give 5,6-dihydrofuro[2,3-*c*]-pyrrol-4-one **10** following a sequence of acylation, intramolecular Diels–Alder cycloaddition and retro-Diels–Alder cycloreversion.[12] Addition of a second dienophile **11** to the reaction mixture should initiate an intermolecular Diels–Alder reaction of furan[6,7e] to give, after directed fragmenta-

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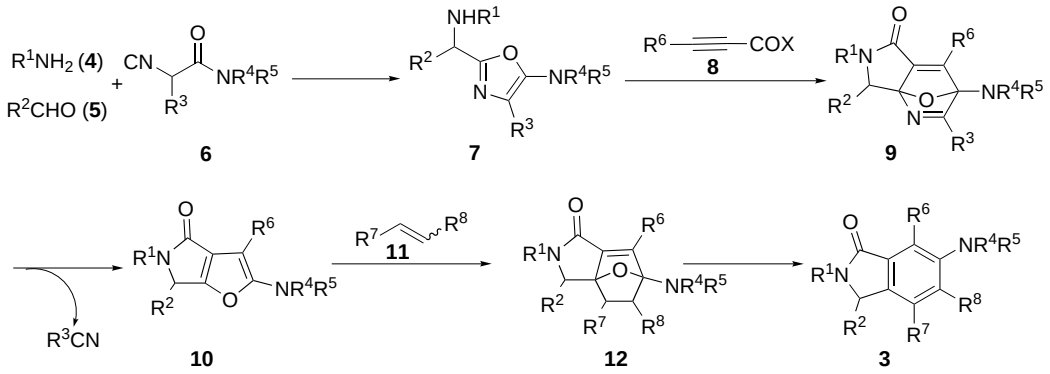
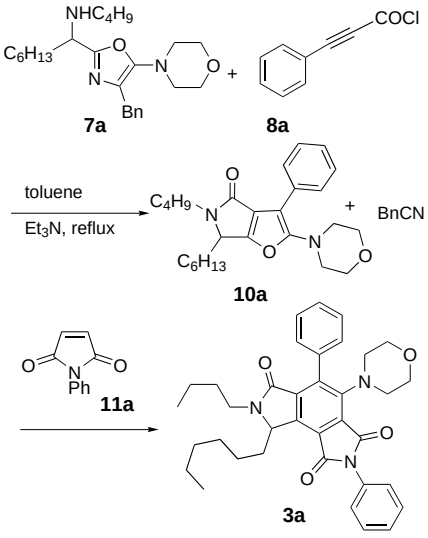


Scheme 1. Five-component synthesis of hexasubstituted benzene.

tion, the hexasubstituted benzenes **3**. The development of conditions for the three-component synthesis of oxazole that are compatible with the subsequent two cycloaddition-based domino processes would enable a five-component synthesis of hexasubstituted benzene **3**. The sequence would allow rapid and efficient construction of structurally complex molecules from readily available starting materials.

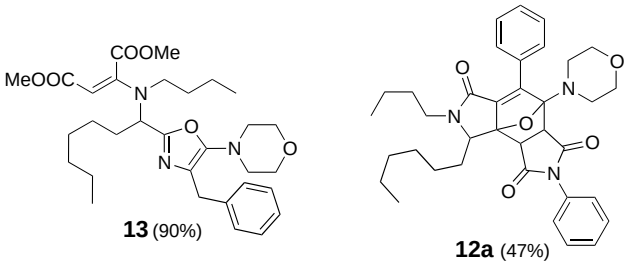
Whereas the cycloaddition of oxazole with acetylene is a well-established method for furan synthesis,[12] the corresponding reaction of 5-aminooxazole was, to the best of our knowledge, unknown. To test the feasibility of the overall process, the reaction between purified 5-aminooxazole **7a** and acyl chloride **8a**[13] was first examined (Scheme 2). The



Scheme 2. From 5-aminooxazole to hexasubstituted benzene.

reaction proceeded smoothly to provide the 5,6-dihydrofuro[2,3-*c*]pyrrol-4-one **10a** (> 95 % yield). A triple domino sequence involving acylation/intramolecular Diels–Alder cycloaddition/retro Diels–Alder cycloaddition could explain the reaction outcome. On the other hand, the reaction of **7a** with dimethylacetylenedicarboxylate (DMAD) provided the Michael adduct **13**; no Diels–Alder cycloaddition took place. Attempts to promote the cycloaddition between **13** and DMAD led only to the recovery of starting materials or to degradation under forcing conditions.

The reaction of the resulting aminofuran with *N*-phenylmaleimide (**11a**) in toluene was next examined. When this reaction was performed at 70 °C in toluene, we were able to isolate the unstable oxa-bridged intermediate **12a** as a



mixture of two diastereomers in 47 % yield. However, on heating the solution in toluene at reflux, hexasubstituted benzene was produced directly. In view of the similar reaction conditions leading to the production of **10a** and **3a**, we reasoned that it might be possible to combine these two domino processes. In the event, heating a solution of oxazole **7a** and acyl chloride **8a** in the presence of triethylamine for 12 h, followed by addition of *N*-phenylmaleimide **11a**, provided **3a** in over 90 % overall yield (Scheme 2).

Encouraged by the efficiency of the two consecutive domino processes, we set out to explore conditions that would enable its combination with the three-component synthesis of 5-aminooxazole **7**. Initial results regarding the quest for this one-pot five-component domino process with lithium bromide gave unsatisfactory results.[14] On the other hand, a stoichiometric amount of ammonium chloride[15] and a catalytic amount of camphorsulfonic acid (CSA, 10 %) were able to promote the five-component domino process, which led to the hexasubstituted benzene **3a** in 40 and 52 % yields, respectively (Scheme 3, X = Cl). Subsequent experiments indicated that the use of pentafluorophenyl ester **8b** (X = OC_6F_5) instead of the acyl chloride **8a** (X = Cl) provided an improved yield of **3a** (67 %). Significantly, in this operationally simple five-component domino process, at least seven reactive functionalities participated in the chemical transformation that led to the concomitant creation of seven chemical bonds (two C–N and five C–C bonds) and a biologically relevant polyheterocycle.

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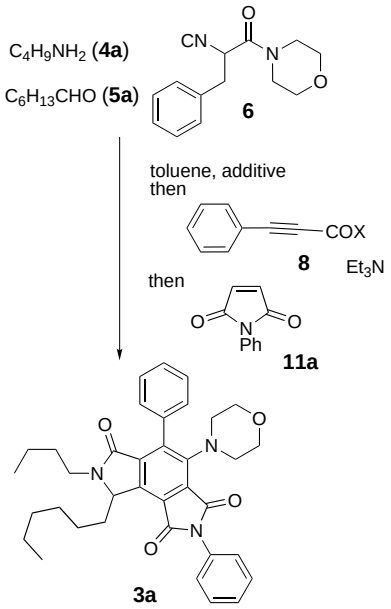
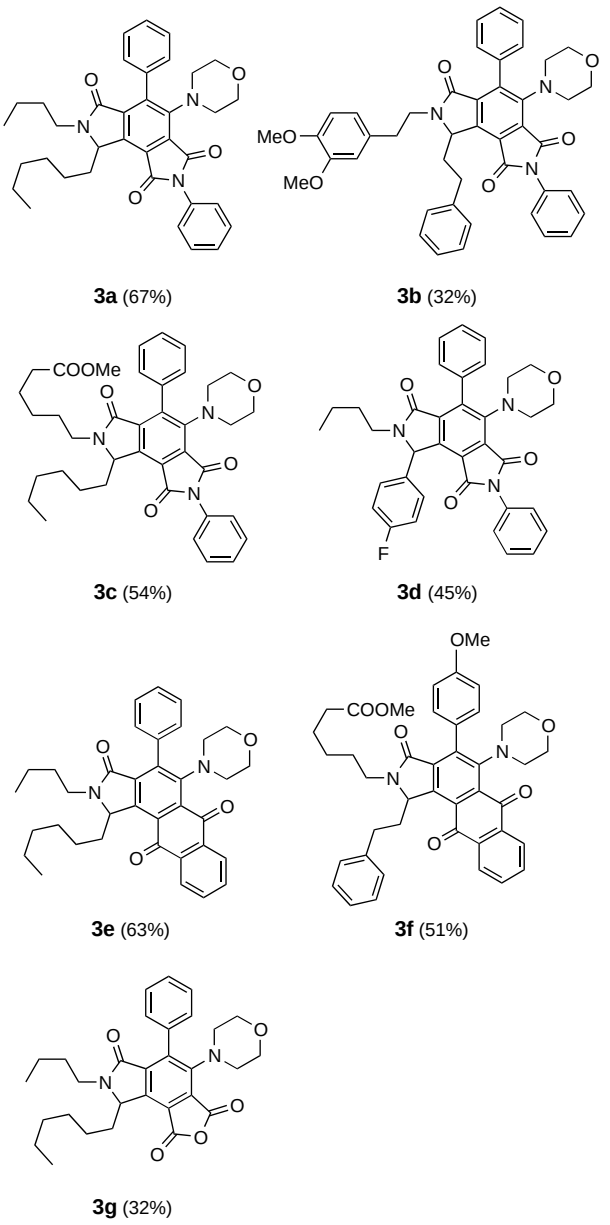


Additive	Equiv.	X	Yield of **3a**
NH_4Cl	1	Cl	40%
CSA	0.1	Cl	52%
CSA	0.1	OC_6F_5	67%

Scheme 3. One-pot five-component synthesis of polyheterocycles with an hexasubstituted benzene core under various conditions.



Scheme 4. Five-component synthesis of polyheterocycles with an hexasubstituted benzene core: selected structures.

The use of three different amines, three aldehydes, one isocyanoacetamide, two pentafluorophenyl 3-arylprop-2-ynoates, and three dienophiles as starting materials allowed the synthesis of the polyheterocycles shown in Scheme 4. The potential and general applicability of this five-component domino process are readily seen from these selected examples.

In conclusion, we have developed a novel five-component domino process for the synthesis of highly functionalized polyheterocycles from simple and readily accessible starting materials. The overall process leads to the creation of seven chemical bonds and delivers five elements of diversity into the compact polyheterocycle, thus providing a large increase in molecular complexity. This constitutes a rare example in which more than four reagents were assembled together to provide a biologically relevant scaffold.[16] The operational simplicity and good chemical yield made these novel heterocycle syntheses highly attractive in diversity-oriented parallel synthesis.[17]

Experimental Section

Typical procedure: Heptanal **5a** (20.0 μL, 0.144 mmol) was added to a solution of butylamine (**4a**, 15.2 μL, 0.156 mmol) in dry toluene (1.0 mL). After the mixture was stirred at room temperature for 30 min, isocyanide **6** (29.0 mg, 0.120 mmol) and camphorsulfonic acid (3.0 mg, 0.012 mmol, 0.1 equiv) were added successively. The reaction mixture was stirred at 60 °C until the disappearance of isonitrile. The reaction mixture was cooled to 0 °C. Et_3N (83.6 μL, 0.60 mmol) was added, followed by a solution of pentafluorophenyl ester **8b** (64.0 mg, 0.2 mmol) in toluene (1.0 mL). Stirring was continued at room temperature for 30 min and at 110 °C for 12 h. *N*-Phenylmaleimide (23.0 mg, 0.132 mmol) was then added. The reaction mixture was stirred for an additional 15 min at 110 °C. After being cooled to room temperature, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The crude reaction mixture was purified by preparative TLC (silica gel, eluent: AcOEt/heptane = 1:2) to give the corresponding hexasubstituted benzene **3a** (46.6 mg, 67 %) as a slight yellow oil. IR: $\tilde{\nu}$ = 3011, 2963, 2931, 2862, 1764, 1714, 1684, 1600, 1502, 1438, 1383, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.58–7.28 (m, 10 H), 5.01 (t, J = 3.5 Hz, 1 H), 3.95 (ddd, J = 6.8, 9.2, 13.8 Hz, 1 H), 3.61 (m, 4 H), 3.00 (ddd, J = 5.0, 8.9, 13.8 Hz, 1 H), 2.95 (m, 4 H), 2.63 (m, 1 H), 2.09 (m, 1 H), 1.62 (m, 2 H), 1.33 (sextet, J = 7.2 Hz, 2 H), 1.19 (m, 6 H), 1.02 (m, 1 H), 0.92 (t, J = 7.2 Hz, 3 H), 0.84 (t, J = 6.6 Hz, 3 H), 0.69 ppm (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.9, 165.8, 165.3, 149.1, 143.6, 137.4, 137.1, 134.6, 131.5, 130.1, 129.7, 129.1, 129.0, 128.2, 128.1, 127.7, 127.6, 126.7, 126.0, 67.0, 57.0, 52.0, 39.7, 31.4, 29.9, 28.9, 28.5, 22.4, 21.8, 20.2, 13.9, 13.7 ppm; MS (ES, positive mode): m/z $[M+H]^+$: 580.0

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Formation and Characterization of the First Monoalumoxane, $LAlO{\cdot}B(C_6F_5)_3$**

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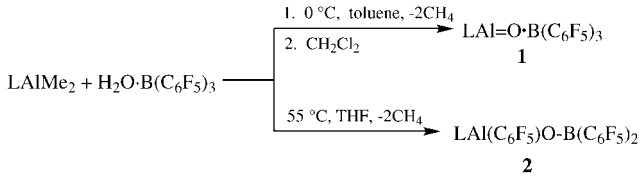
Ana Mirela Neculai, Jörg Magull, Bernhard Walfort, and Dietmar Stalke

Dedicated to Professor Heribert Offermanns on the occasion of his 65th birthday

It has been shown that alumoxanes of the general formula $(RAlO)_n$ for $n > 1$ can be obtained by the controlled reaction of organoaluminum compounds with either water or water contained in hydrated salts or $(Me_2SiO)_3$.[1] Although the simplest member of the series, namely (RAlO), was predicted to be obtainable based on the analogy with aluminum imides,[2] its formation and characterization has remained elusive, presumably because it implies the presence of an Al–O double bond, which is likely to be very unstable even though π interactions between Al and O atoms have been invoked by several groups.[3] However, compounds with such bonds may be either sterically (by using bulky ligands bonded to the aluminum) or electronically (by using Lewis acids) stabilized. Our approach for the stabilization was to use $H_2O{\cdot}B(C_6F_5)_3$, which has been shown to act as a strong Brønsted acid,[4] and whose ability to protonate M–R bonds has been verified.[5] Furthermore if a monoalumoxane is formed, $B(C_6F_5)_3$ may hinder the aggregation owing to its strong Lewis acid character.[6]

Indeed, the reaction of $LAlMe_2$ (where L is a monoanionic β-diketiminato ligand, Scheme 1)[7] and $H_2O{\cdot}B(C_6F_5)_3$ in toluene gave $LAlO{\cdot}B(C_6F_5)_3$ (**1**), which was filtered off at room temperature and crystallized from dichloromethane (−26 °C). In contrast, when the same reagents were allowed to react in THF at 55 °C for 2 h, after the solvent had been removed, an oily product was formed which crystallized as an isomer of **1**, formulated as $LAl(C_6F_5)OB(C_6F_5)_2$ (**2**; Scheme 1).



where L = $Et_2NCH_2CH_2NC(Me)CHC(Me)NCH_2CH_2NEt_2$

Scheme 1. Synthesis of compounds **1** and **2**.

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