Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 7224

www.rsc.org/obc

PAPER

Practical three-component synthesis of crowded arenes with donor–acceptor substitution†

Robert Fichtler, Jörg-M. Neudörfl and Axel Jacobi von Wangelin*

Received 17th June 2011, Accepted 19th July 2011
DOI: 10.1039/c1ob05984j

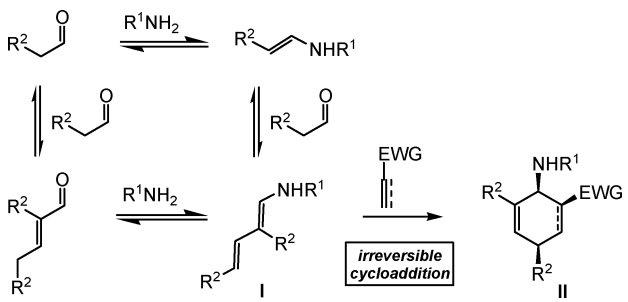
An operationally simple two-step synthesis of substituted anilides has been developed. The methodology utilizes carboxamides, aldehydes, and olefins (or alkynes) as cheap starting materials and relies upon the sequential combination of condensation, cycloaddition, and oxidation reactions. The intermediate cycloadducts display various functional groups (*e.g.* Br, OAc, NR_2, COR, Cbz) for further chemical manipulation at the ring periphery or core. Upon oxidation with MnO_2, highly crowded anilides with up to four further substituents (alkyl, aryl, carboxylate, cyano, nitro, bromo) can be prepared in good overall yields.

Introduction

Multi-component reactions have attracted considerable interest owing to their potential to assemble highly diversified and complex molecular architectures from simple starting materials in one synthetic operation. The adoption of such strategies comes along with the minimization of both waste production and expenditure of human labour.[1] Diels–Alder reactions[2] are one of the key methods for the rapid generation of functionalized six-membered rings in a cycloaddition process which can also be applied to the synthesis of functionalized arenes *via* subsequent skeletal rearrangements, eliminations or oxidative transformations.[3] The latter strategy is especially attractive with cheap and readily available oxidants. We wish to report on the facile preparation of highly substituted *N*-acyl aniline derivatives from cheap starting materials in two synthetic steps involving a multi-component cycloaddition and an oxidation (Scheme 1). The resultant highly modular aromatic molecules contain a donor–acceptor substituted arene core (anthranilic acid derivative) which is central to various applications as fine chemicals, dyes, pigments, and materials.[4]

Scheme 1 Two-step synthesis of anthranilic acid derivatives.

We have recently identified conditions for selective three-component reactions of simple aldehydes, carboxamides, and dienophiles to give functionalized aminocyclohexenes or aminocyclohexadienes (Scheme 2).[5] The protocol involves initial acid-catalyzed reaction of the carboxamide with an enolizable aldehyde to give an equilibrium of various condensation and aldol products, with each of the components being formed in rather low yields (~25% of aminodiene **I**).[6] The addition of an electron-deficient dienophile triggers the selective consumption of **I** in an irreversible cycloaddition to selectively drive the equilibria to the aminodiene side, thereby providing a high-yield synthesis of the corresponding cycloadducts **II**.[6] The overall three-component reaction relies on simple starting materials (amide, aldehyde, dienophile) and results in the generation of four new bonds in one synthetic operation with high *endo*-stereocontrol. The high utility of such carbocyclic building blocks has been demonstrated in the synthesis of fine chemicals, pharmaceuticals, and materials.[7]



Scheme 2 Domino condensation–cycloaddition mechanism.

Results and discussion

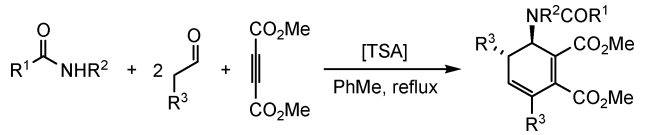
Synthesis of *pseudo*-four-component aminocyclohexadienes from aldehydes bearing an α-CH_2 group

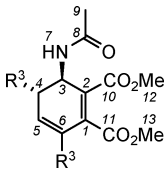
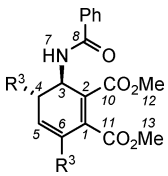
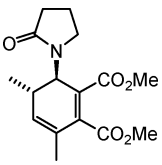
Table 1 shows a series of *pseudo*-four-component cycloadducts from reactions of a carboxamide and dimethyl acetylenedicarboxylate (DMAD) with two molecules of aldehyde in refluxing

Department of Chemistry, University of Cologne, Greinstr. 4, 50939, Köln, Germany. E-mail: axel.jacobi@uni-koeln.de; Fax: +49 221 470 5057; Tel: +49 221 470 6122

† Electronic supplementary information (ESI) available: Experimental procedures, analytical data of all new compounds. CCDC reference numbers 832706–832713. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05984j

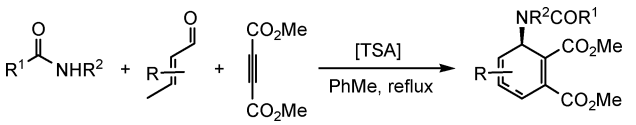
Table 1 *Pseudo*-four-component cyclohexadienes from aldehydes[a]

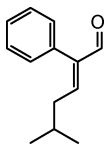
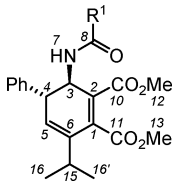
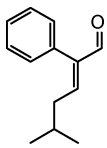
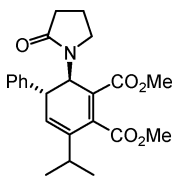
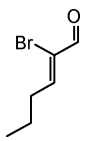
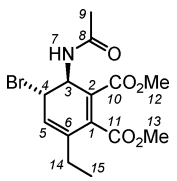


R^1, R^2	R^3	Product		Yield [%]
Me, H	Me		**1**	69
	Et		**2**	75
	Bn		**3**	66
	i-Pr		**4**	88
	Ph		**5**	49
Ph, H	Bn		**6**	63
	Ph		**7**	52
–$(CH_2)_3$–	Me		**8**	59

[a] Amide (1 equiv.), aldehyde (2 equiv.), DMAD (1 equiv.), *p*-TSA·H_2O (3 mol%) and Ac_2O (1 equiv.) in PhMe were heated for 16 h at 110 °C.

Table 2 Three-component cyclohexadienes from unsaturated aldehydes[a]



R^1, R^2	Aldehyde	Product		Yield [%]
Me, H			**9**	88
2-BrC_6H_4, H			**10**	89
Ph, H			**11**	87
$BrCH_2$, H			**12**	66
–$(CH_2)_3$–			**13**	89
Me, H			**14**	38

[a] Carboxamide (1 equiv.), aldehyde (1 equiv.), DMAD (1.5 equiv.) and *p*-TSA·H_2O (3 mol%) in PhMe were heated for 16 h at 110 °C.

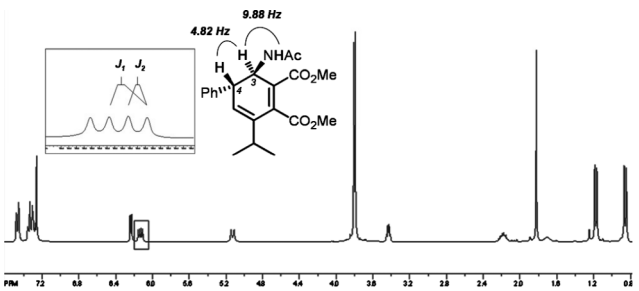
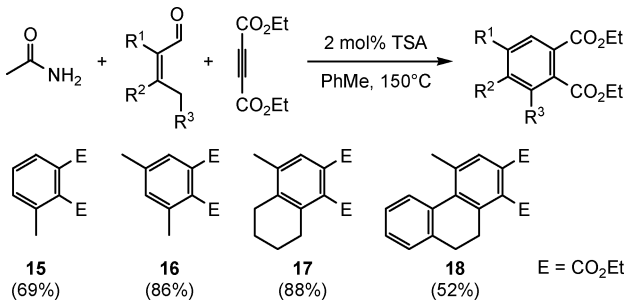


Fig. 1 ^{1}H NMR spectrum and $^3J_{H,H}$ coupling constants of **9**.

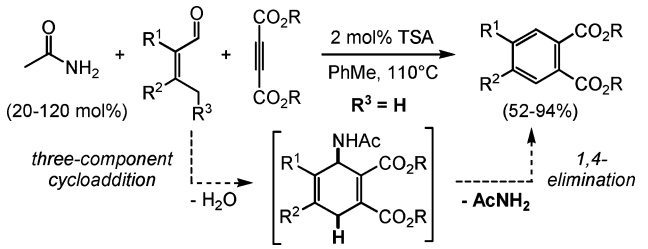
toluene under catalysis of *p*-toluenesulfonic acid monohydrate (TSA·H_2O)[8] The intermediate formation of the aminodiene species **I** can also be viewed as a selective telomerization of two molecules of aldehyde with the carboxamide (with suppression of further condensations to longer aldol-type products).[6,9] The resultant penta-substituted amidocyclohexadienes **1–8** contain two equal substituents in a 1,3-relation due to the incorporation of two aldehyde molecules. The double bonds of the cyclohexadiene products are subject to thermodynamic equilibration under the reaction conditions (TSA, 110 °C) to give a conjugated diene moiety. Vicinal amino and alkyl moieties adopt a *trans* configuration as evidenced by the $^3J_{HH}$ coupling constants (~ 5 Hz, see also Fig. 1).

Synthesis of aminocyclohexadienes and phthalates from α,β-unsaturated aldehydes

Enhanced product diversity was attained upon employment of α,β-unsaturated aldehydes. Table 2 shows a selection of six cycloadducts from reactions of primary or secondary carboxamides with DMAD and α,β-unsaturated aldehydes.[10] The presence of a conjugated diene moiety and a *trans* substitution in **9–14** was confirmed by ^{1}H NMR analysis.[11] Higher temperatures (>130 °C) led to low yields of the target compounds (<20%), but instead facilitated acylamine elimination from the intermediate cyclohexadienes. Thus, tri-, tetra-, and penta-substituted diethyl phthalates (**15–18**) were prepared in good yields after 20 h at 150 °C from α,β-unsaturated aldehydes,[12] acetamide, and diethyl acetylenedicarboxylate (Scheme 3). It is interesting to note, that one-pot reactions employing crotonaldehyde derivatives without γ-substituents (Scheme 4, R^3 = H) afforded phthalates *via* sequential aminodiene cycloaddition and formal 1,4-*syn*-elimination of acetamide at lower temperatures (110 °C). This explains why the desired amidocyclohexadienes could not be



Scheme 3 Synthesis of phthalates under high temperature conditions.[10]



Scheme 4 Acetamide-mediated synthesis of phthalates *via* formal 1,4-elimination.[10]

prepared from crotonaldehydes (R^3 = H) under the standard reaction conditions. Such aromatizations can be used for the facile synthesis of substituted phthalates, even under acetamide catalysis (>20 mol%). The operational simplicity of this procedure has been demonstrated by processing the reaction and the downstream product analysis in fully automated fashion by a bench top robot (Scheme 4).[10]

Synthesis of three-component aminocyclohexenes from α,β-unsaturated aldehydes

We have then extended the scope of the three-component reaction to also include olefins as dienophiles (Table 3). Cycloadditions with symmetrical maleimides proceeded with high stereocontrol (*endo* : *exo* > 95 : 5) for most products. With bulky amides (R^1 = Phenyl, *o*-Aryl *etc.*), the *exo* diastereomer becomes slightly less disfavoured.[13] The choice of aldehyde determines the substitution pattern of the resultant 1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl carboxamide structures in positions 4, 5, and 6 (see for example methyl derivatives **19–22**). The reaction with citral (commercial mixture of geranial and neral) afforded two regioisomers in 39% (**23a**) and 26% (**23b**)[14] yield. Substituted 1-bromo-1-cyclohexenes (**24**, **25**) were obtained from reactions with 2-bromocrotonaldehydes.[15] Benz-anellated heteroaromatic substituents were incorporated into the product structures of **26** and **27**.

The standard reaction conditions tolerate various carboxamides as reagents. Employment of 2-pyrrolidinone gave three-component adduct **28** with a tertiary amide moiety. Benzyloxycarbonyl (Cbz) protection of the amino function has been realized for **29–31**, while **32** contains an *N*,*N*-dimethylurea terminus. The stereochemical outcome of the reactions has been analyzed for all cycloadducts by ^{1}H NMR spectroscopy based upon H,H/H,C-COSY and $^3J_{HH}$ coupling constants. Fig. 2 shows the crystal structure of bromocyclohexene **24** which establishes the expected

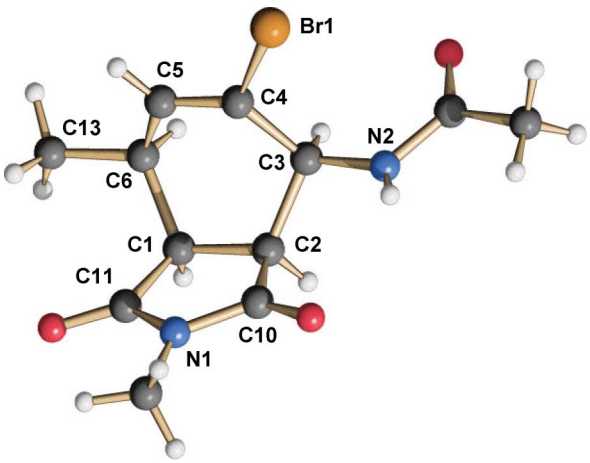
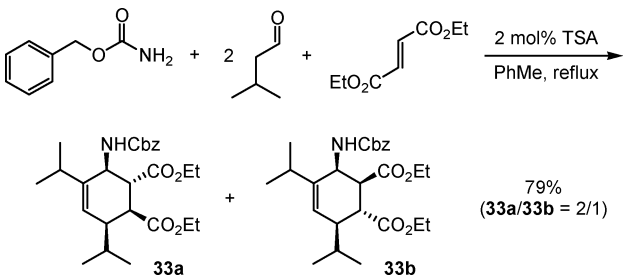


Fig. 2 Crystal structure of **24**. Selected bond lengths [Å] and angles [°]: C1–C2 1.547(5), C2–C11 1.521(2), C3–N2 1.443(5), C4–C5 1.308(4), C4–Br1 1.899(3), C6–C1–C10 113.82(0), C11–C2–C3 112.41(0), C3–C4–Br1 117.53(0), C11–C2–C3–N2 −53.80(1), N2–C3–C4–Br1 −14.05(1), C13–C6–C1–C10 52.76(1).

endo-geometry with an all-*syn* substitution pattern about the central cyclohexene ring (Table 7). Employment of diethyl fumarate resulted in the formation of two inseparable diastereomers **33a** and **33b** under the standard conditions (Scheme 5).

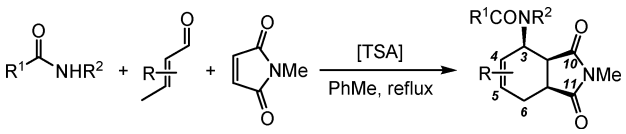


Scheme 5 Synthesis of two diastereomers from diethyl fumarate.

The reactions discussed so far involved symmetrical dienophiles with two identical electron-withdrawing substituents. A normal electron-demand Diels–Alder reaction, the second step of the underlying domino sequence, is usually a concerted process obeying the rules of orbital symmetry. On the other hand, related reactions with unsymmetrical dienophiles containing only one electron-withdrawing substituent might favour a stepwise (Michael-type) pathway *via* polar intermediates. Reactions with acrylonitrile and 2-benzylidene malononitrile, however, gave cyclohexenes **34** and **35** as *endo*-adducts in moderate yields (Table 4). Employment of *trans*-2-nitrostyrene afforded the cycloadduct **36** in 79% yield containing the vicinal nitrogen-based substituents (NHAc, NO_2) in a *syn* relation. The crystal structure of **36** is shown in Fig. 3 (see also Table 7). The observed stereocontrol could be a consequence of an intramolecular hydrogen bonding interaction between the acetamido and nitro groups in the transition state. Related reactions with (more nucleophilic) secondary amines have been shown to proceed *via* a stepwise Michael-type mechanism involving thermodynamic equilibration to give the corresponding *trans*-stereoisomer.[16]

The generation of the reactive diene intermediates by reaction of a (nucleophilic) amide with an unsaturated aldehyde can be

Table 3 Synthesis of three-component cyclohexadienes from α,β-unsaturated aldehydes and *N*-methyl maleimide[a]



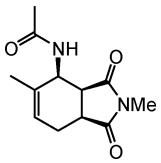
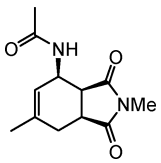
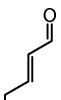
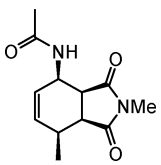
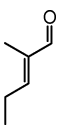
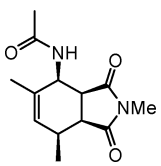
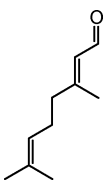
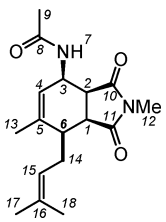
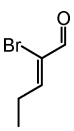
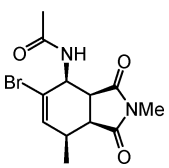
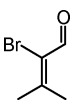
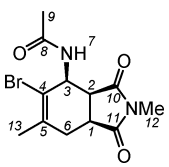
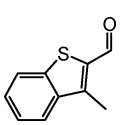
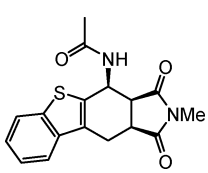
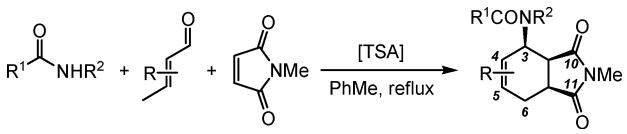
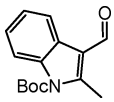
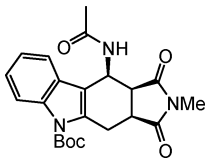
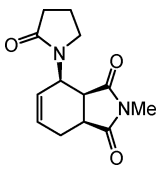
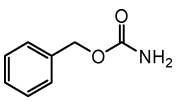
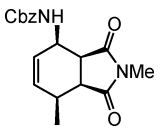
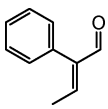
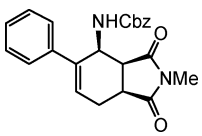
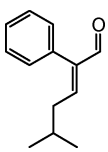
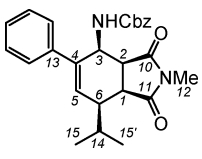
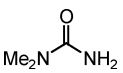
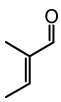
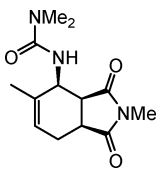
Amide	Aldehyde	Product		Yield [%]
			**19**	76
			**20**	76
			**21**	54
			**22**	76 (80)[b]
			**23a**	39[c] (*syn* : *anti* = 2 : 1)
			**24**	70
			**25**	71
			**26**	46[d]

Table 3 (*Contd.*)



Amide	Aldehyde	Product		Yield [%]
			**27**	27[e]
			**28**	77
			**29**	98
			**30**	98
			**31**	83
			**32**	75

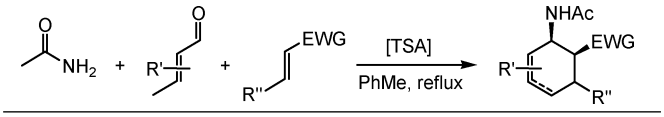
[a] Equimolar carboxamide, aldehyde, and *N*-methylmaleimide with *p*-TSA·H_2O (3 mol%) in toluene were heated at 110 °C for 20–40 h. Oligomeric aldehyde by-products were detected by GC–MS. [b] In brackets reaction from propionaldehyde. [c] 26% regioisomer (**23b**).[14] [d] 40% aldehyde recovered. [e] 25% aldehyde recovered.

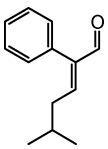
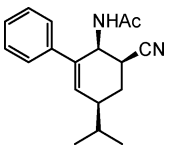
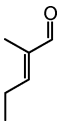
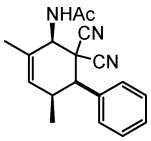
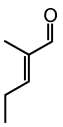
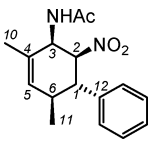
modulated to an electrophilic trapping of the aldehyde by acetic anhydride (Ac_2O). The resultant acetoxydienes constitute another class of activated heteroatom-functionalized dienes for Diels–Alder reactions with electron-deficient dienophiles.[17] Scheme 6 illustrates the reaction of 3,3-dimethylacrolein with *trans*-β-nitrostyrene in the presence of Ac_2O under otherwise identical conditions. Cyclohexenyl acetate **37** was isolated in 69% yield as a mixture of two *endo*-diastereomers (7 : 1). The major isomer bears the acetate and nitro groups in a *syn* relation (*pseudo*-anomeric, axial OAc); the minor is the C1 epimer.

Oxidation reactions

Dehydrogenative oxidation of the synthesized aminocyclohexadienes and aminocyclohexenes would render a straightforward access to polyfunctional anilines which are important substructures in pharmaceuticals, herbicides, dyes, and materials.[18] Several methods for the aromatization of carbocycles have been reported, including precious metal catalysts (Pt, Pd, Ni), elemental sulfur or selenium, quinones (*e.g.* chloranil, DDQ), oxygen/air, manganese oxide, selenium oxide, chromic acid, and activated charcoal.[19]

Table 4 Synthesis of three-component cyclohexenes from α,β-unsaturated aldehydes and unsymmetrical dienophiles[a]



Amide	Aldehyde	Product		Yield [%]
			**34**	25[b]
			**35**	46[c] (*syn* : *anti* 3 : 1)
			**36**	79[d]

[a] Amide (1 equiv.), aldehyde (1 equiv.), *p*-TSA·H_2O (3 mol%) heated in toluene at 110 °C for 24 h. [b] Acrylonitrile as dienophile (3 equiv.), polymerization of dienophile observed. [c] 2-Benzylidene malononitrile as dienophile (1 equiv.) [d] *trans*-2-Nitrostyrene as dienophile (1 equiv.)

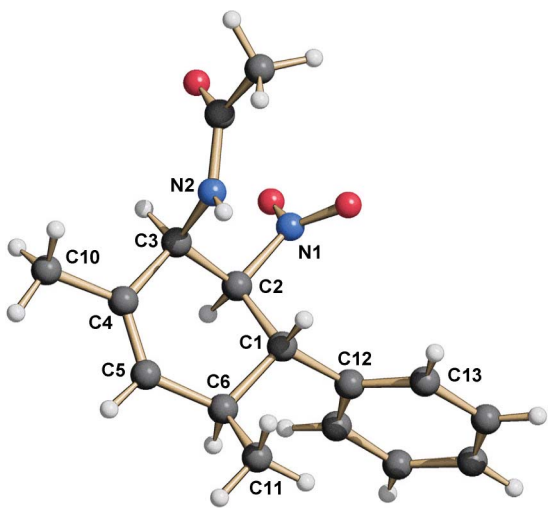
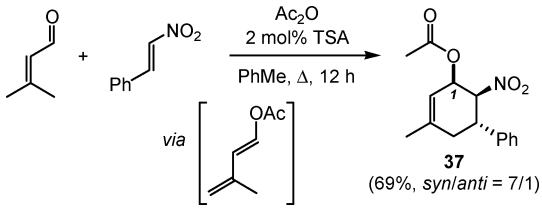


Fig. 3 Crystal structure of **36**. Selected bond lengths [Å] and angles [°]: C1–C2 1.524(2), C2–C3 1.539(2), C4–C5 1.326(0), C1–C12 1.521(0), C2–N1 1.508(0), C3–N2 1.461(0), C12–C1–C2 114.37(0), N1–C2–C3 108.74(0), C2–C3–N2 113.21(0), C10–C4–C5 123.39(0), C6–C1–C12–C13 –115.13(0), C11–C6–C1–C12 71.16(0), C12–C1–C2–N1 –50.35(1), N1–C2–C3–N2 –56.46, N2–C3–C4–C10 74.69(0).

A subsequent aromatization of the three-component amino-substituted cycloadducts would also afford identical products from diastereomeric mixtures and thus obviate laborious chromatographic separation of the stereoisomers and enhance the overall yield of the two-step methodology. We focused on rather



Scheme 6 Synthesis of diastereomeric cyclohexenyl acetates *via* intermediate 3-methylbutadienyl acetate.

environmentally friendly and cheap oxidants and were delighted to find that oxidation of the synthesized amidocyclohexadienes was best effected with commercial manganese dioxide (MnO_2) in refluxing toluene.[20] The methodology shows promise for the synthesis of crowded arenes with diverse substitution patterns. A series of 25 polysubstituted anilides have been prepared from MnO_2-mediated oxidative aromatization of three-component amidocyclohexadienes (Table 5) and amidocyclohexenes (Table 6) in good to excellent yields. A larger excess of MnO_2 was required for the aromatization of aminocyclohexenes (mostly 5 equiv.). No difference in activity was found for commercial, freshly prepared (from $MnSO_4$, $KMnO_4$ and NaOH),[21] or freshly activated MnO_2 (oven dried at 130 °C with 4 Å molecular sieves). The formation of over-oxidized products (benzoquinones, azobenzenes, oligoanilines) was not observed. Benzoquinone and 2,3-dichloro-5,6-dicyanoquinone (DDQ) gave far inferior results (<25% yields for oxidations of model substrates **1** and **19**). Reactions of **1** and **2** in the presence of catalytic amounts of Pd/C (10 mol%) and sacrificial cyclohexene (1.5 equiv.) at 100 °C led to major decomposition, with only 15–20% of the desired anilides being formed. The remarkably good yields for oxidations to give crowded substrates such as **40–42** and **44–48** document the efficiency of the MnO_2-based methodology. Dibenzyl derivative **3** underwent acetamide elimination under the reaction conditions to cleanly give dimethyl 3,5-dibenzyl-phthalate in 90% yield. The crystal structure of penta-substituted benzamidophthalate **46** is shown in Fig. 4 (see also Table 7). Bromocyclohexene **14** (Table 5) gave clean conversion to the corresponding bromobenzene **49** in 70% yield. Benzothiophene **26** showed no conversion, while indole derivative **27** gave a complex mixture of products, presumably initiated by (indole)-*N*-assisted acetamide elimination. Cbz-protected aminocyclohexene **29** gave the anilide **60** in 55% yield; the bulkier 4-phenyl analogue **30** showed only low conversion (<10%) even after 48 h in refluxing toluene. Urea derivative **32** underwent deacylation to give aniline **62**. Oxidation of amidonitrocyclohexene **35** gave dinitrogen-substituted biaryl derivative **64** in 75% yield. The related acetate **36** underwent formal elimination of acetic acid (HOAc) to give *o*-nitrobiphenyl **65** in 79% yield (Scheme 7).

Conclusions

We have applied an operationally simple one-pot protocol to the synthesis of multi-substituted carbocycles upon three-component reaction of simple carboxamides, aldehydes, and dienophiles (olefins or alkynes). The resultant amidocyclohexenes and amidocyclohexadienes were mostly obtained as single diastereomers from a selective *endo*-cycloaddition in good to excellent yields. The thermal acid catalyzed reaction tolerates ester, nitrile, ether,

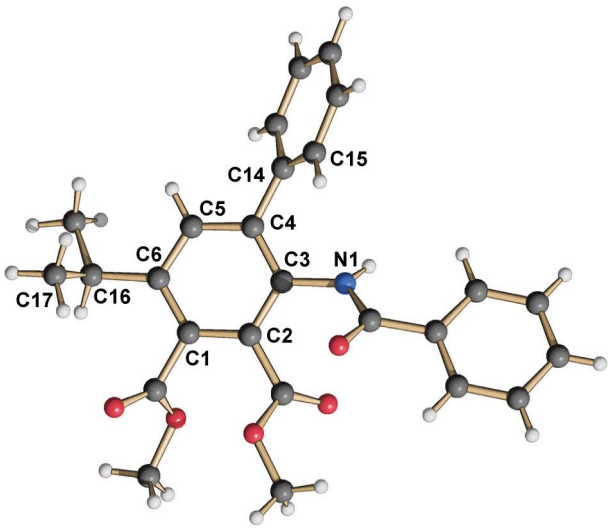
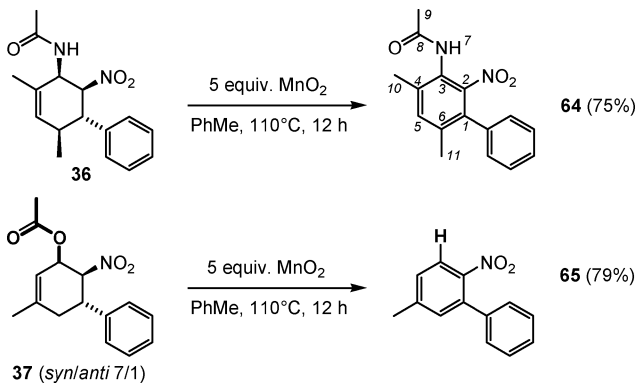


Fig. 4 Crystal structure of **46**. Selected bond lengths [Å] and angles [°]:C1–C2 1.398(2), C3–N1 1.426(0), C4–C14 1.486(0), C6–C16 1.525(0), C2–C3–N1 120.08(0), C2–C4–C14 123.72(0), C5–C6–C16 120.76(0), C1–C2–C3–N1 –177.28(0), C2–C3–C4–C14 –178.21(0), C3–C4–C14–C15 –56.38(0), C5–C6–C16–C17 –89.65(0).



Scheme 7 Oxidations of nitrocyclohexenes **36** and **37**.

chloro, bromo, thioether, amine, urea, and carbamate substituents. Upon wide variations of the starting materials, the synthesis allows access to diverse cycloadducts in a combinatorial fashion. The three-component carbocycles can be subjected to oxidative aromatizations in the presence of MnO_2 to give crowded anilides[22] in good to excellent yields. The tri-, tetra-, and penta-substituted arenes constitute building blocks with interesting stereoelectronic and synthetic properties: high steric encumbrance at the arene core, donor–acceptor substitution, strong fluorescence of the aminophthalimide derivatives,[23] a synthetically useful inherent anthranilic acid motif, access to substituted β-amino acids[7a] The overall two-step synthesis is highly modular and operates under practical reaction conditions with cheap starting materials and reagents (1st step: catalytic TSA, toluene as solvent; 2nd step: MnO_2 as oxidant, toluene as solvent).

Experimental section

General

Unless otherwise noted, all synthesized cycloadducts are racemic mixtures of one diastereomer. For reasons of clarity, only one enantiomer is depicted in the schemes. For atom numbering used in the spectroscopic data assignment, see chemical structures in Schemes and Tables above. All chemicals were purchased from commercial suppliers and used without further purification unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 600 (600.20 and 150.94 MHz), a Bruker DRX 500 (500.13 and 125.77 MHz) and a Bruker Avance 300 (300.13 and 75.48 MHz) at 298 K. Chemical shifts (δ in ppm) are referenced to tetramethylsilane (TMS). Abbreviations for ^{1}H-NMR data: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet), q* (apparent quartet), m* (apparent multiplet). Peaks were assigned based on H,H-COSY, H,C-HMQC, and H,C-HMBC. IR-ATR spectroscopy was performed on a Perkin–Elmer 100 Paragon FT-IR. ESI-MS were measured with a Finnigan MAT 900S and an Agilent LC/MSD VL G1956A, respectively. EI-MS were measured with a Finnigan Incos 50 Galaxy and a Finnigan MAT 95, respectively (ionization 70 eV). Exact masses (HR-MS) were determined by peak matching method. Crystal structure data were collected on a Nonius Kappa CCD diffractometer using monochromated Mo-Kα radiation, structures refined by shelxs97 and shelxl97.[24]

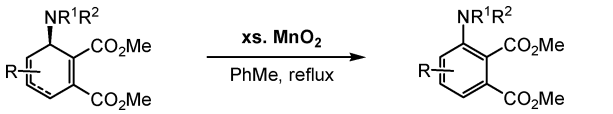
General procedure for the synthesis of cycloadducts from aldehydes bearing an α-CH_2 group

A 50 mL test tube was charged with carboxamide (6 mmol), aldehyde (12 mmol), the dienophile (6 mmol), *p*-toluenesulfonic acid monohydrate (3 mol%), acetic anhydride (6 mmol), and toluene (8 mL). The tube was sealed with a septum and the reaction stirred at 110 °C oil bath temperature. After 24 h, the solvent and other volatile compounds were removed by oil pump vacuum. The crude product was purified by SiO_2 flash column chromatography (ethyl acetate (ea) : cyclohexane (ch)) or crystallized from solution (for details see below).

Dimethyl 6-acetylamino-3,5-diisopropylcyclohexa-1,3-dien-1,2-dicarboxylate (4). Work-up: SiO_2, ea : ch 2 : 1, R_f 0.35, colorless oil; yield: 88%. IR (ATR): $1/\lambda$ [cm^{-1}] 3385 (w), 2948 (w), 2354 (w), 1721 (s), 1680 (s), 1490 (m), 1432 (m), 1367 (w), 1259 (s), 1065 (w), 1031 (w); LR-MS (pos. ESI, MeOH, CH_2Cl_2): *m/z* 360 [M+Na]$^+$, 259; HR-MS (ESI, [u]): found: 360.179 [M+Na]$^+$, calcd: 360.1787; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.59 (d, 1H, 4.1 Hz, H-5), 5.47 (dd, 1H, 9.9/4.5 Hz, H-3), 5.05 (d, 1H, 9.9 Hz, H-7), 3.78 and 3.73 (2 s, 6H, H-12, H-13), 3.17 (q*, 1H, 4.1 Hz, H-4), 2.33 (sept, 1H, 7.0 Hz, H-16), 2.06 (m, 1H, H-14), 1.96 (s, 3H, H-9), 1.06 (m, 9H) and 0.73 (d, 3H, 6.7 Hz) (H-15, H-15′, H-17, H-17′); ^{13}C-NMR (150 MHz, APT, $CDCl_3$): δ 169.4 (C-8), 168.4 and 166.8 (C-10, C-11), 143.9 (C-6), 141.5 (C-1), 132.3 (C-2), 118.5 (C-5), 52.5 and 52.4 (C-12, C-13), 45.1 (C-3), 44.0 (C-4), 30.2 and 29.6 (C-14, C-16), 23.5, 22.7, 21.5, 21.1 (C-15, C15′, C17, C-17′), 17.3 (C-9).

Dimethyl 6-benzoylamino-3,5-diphenylcyclohexa-1,3-dien-1,2-dicarboxylate (7). Work-up: SiO_2, ea : ch 1 : 1; R_f 0.30; white solid; yield: 52%. Mp 76 °C; IR (ATR): $1/\lambda$ [cm^{-1}] 3340 (w), 3033 (w), 2940 (w), 2366 (w), 2240 (w), 1717 (s), 1652 (s), 1513 (s), 1481 (s), 1430 (m), 1264 (s), 1156 (m), 1070 (m), 906 (m),883 (m), 696 (s); LR-MS (pos. ESI, MeOH, CH_2Cl_2): *m/z* 490 [M+Na]$^+$, 347, 315, 303, 244, 105; HR-MS (ESI, [u]): found: 490.163 [M+Na]$^+$, calcd: 490.1631; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.57 (m, 2H, Ph), 7.47–7.23 (m, 13H, Ph), 6.40 (dd, 1H, 9.5./5.7 Hz, H-3),

Table 5 MnO_2-mediated aromatization of aminocyclohexadienes[a]



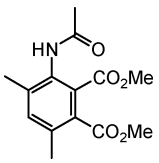
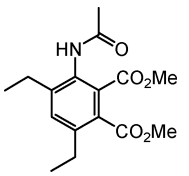
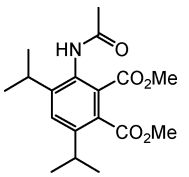
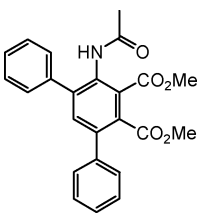
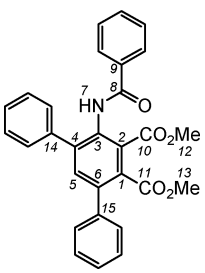
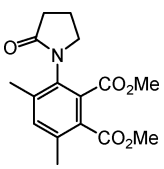
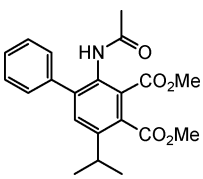
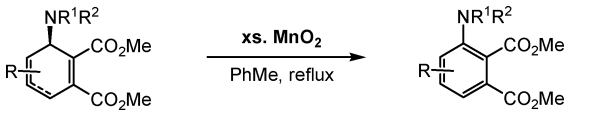
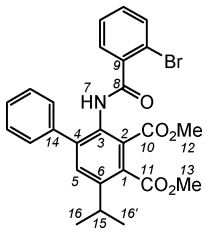
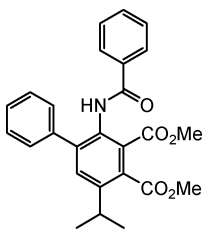
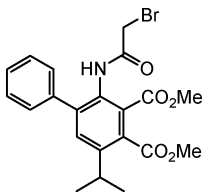
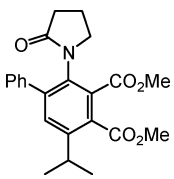
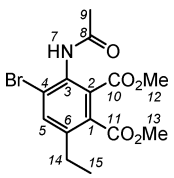
Cycloadduct	Arene		Yield [%]
1		**38**	96[b,e]
2		**39**	84[b,e]
4		**40**	79[d,g]
5		**41**	84[b,f]
7		**42**	65[b,g]
8		**43**	65[b,f]
9		**44**	88[b,e]

Table 5 (*Contd.*)

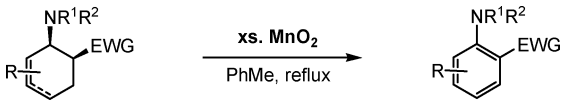


Cycloadduct	Arene		Yield [%]
10		**45**	86[b,e]
11		**46**	94[b,e]
12		**47**	44[c,h]
13		**48**	63[b,e]
14		**49**	70[b,e]

[a] Cycloadduct (1 equiv.) and MnO_2 (85%, 3–10 equiv.) were heated in toluene (2.0–20 mL $mmol^{-1}$ cyclohexene) at 110 °C for 5–48 h. With bulky aminocyclohexadienes, conversions were not quantitative. In some cases, elimination of the amide was observed (~10%). [b] 3 equiv. MnO_2. [c] 6 equiv. MnO_2. [d] 10 equiv. MnO_2. [e] 5 h. [f] 15 h. [g] 24 h. [h] 48 h.

6.34 (d, 1H, 4.5 Hz, H-5), 5.95 (d, 1H, 9.5 Hz, H-7), 4.67 (m, 1H, H-4), 3.80 and 3.61 (2 s, 6H, H-12, H-13); ^{13}C-NMR (75 MHz, APT, $CDCl_3$): δ 167.4 (C-8), 140.1 (C-9), 137.1, 137.0, 134.5, 133.7, 133.2 (C-1, C-2, C-6, C-14, C-15), 131.7, 129.3, 128.8, 128.7, 128.5, 128.3, 128.1, 127.6, 127.2, 127.0, 126.1 (CH_{arom} and C-5), 52.9 and 52.4 (C12, C-13), 45.6 (C-3), 44.1 (C-4); C-10, C-11 and 4 CH_{arom} obscured.

Table 6 MnO_2-mediated aromatization of aminocyclohexenes[a]



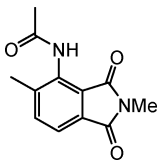
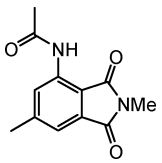
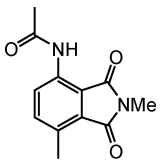
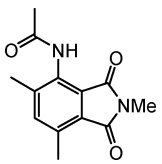
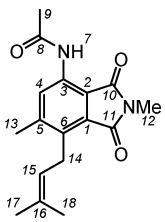
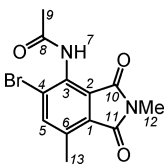
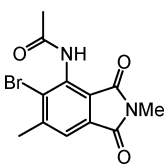
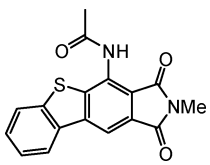
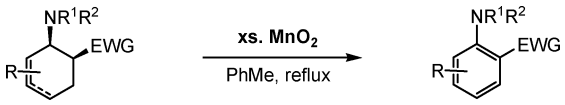
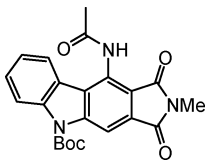
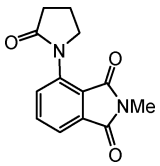
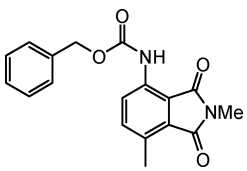
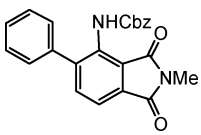
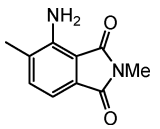
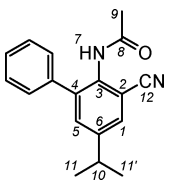
Cycloadduct	Arene		Yield [%]
19		**50**	65[c,g]
20		**51**	58[c,f]
21		**52**	74[b,f]
22		**53**	66[c,f]
23a		**54**	71[c,e]
24		**55**	68[c,g]
25		**56**	<5[c,d,h]
26		**57**	no conv.[c,g]

Table 6 (*Contd.*)



Cycloadduct	Arene		Yield [%]
27		**58**	decomp.[c,f]
28		**59**	72[b,e]
29		**60**	55[b,f]
30		**61**	<10% conv.[c,g]
32		**62**	78[c,f]
34		**63**	75[c,g]

[a] Cycloadduct (1 equiv.) and MnO_2 (85%, 5–10 equiv.) were heated in toluene (2.0–20 mL $mmol^{-1}$ cyclohexene) at 110 °C for 12–48 h. With bulky aminocyclohexenes, conversions were not quantitative. In some cases, elimination of the amide was observed (~10%). [b] 5 equiv. MnO_2. [c] 10 equiv. MnO_2. [d] 12 h. [e] 19 h. [f] 24 h. [g] 48 h. [h] Mostly decomposition.

General procedure for the synthesis of cycloadducts from α,β-unsaturated aldehydes

A 50 mL test tube was charged with carboxamide (4 mmol), aldehyde (4 mmol), the dienophile (4 mmol), *p*-toluenesulfonic acid monohydrate (3 mol%), and toluene (6 mL). The tube was sealed with a septum and the reaction stirred at 110 °C oil bath temperature. After 24 h, the solvent and other volatile compounds were removed by oil pump vacuum. The crude product was purified by SiO_2 flash column chromatography (ethyl acetate (ea) : cyclohexane (ch)) or crystallized from solution (for details see below).

Dimethyl 6-(2-bromobenzoyl)amino-3-isopropyl-5-phenylcyclohexa-1,3-dien-1,2-dicarboxylate (10). Work-up: SiO_2, ea : ch 1 : 2, R_f 0.22; yellow solid; yield: 89%. Mp 65 °C; IR (ATR): $1/\lambda$ [cm^{-1}] 3423 (w), 3340 (w), 2946 (w), 1721 (s), 1666 (s), 1503 (s), 1433 (m), 1263 (s), 1163 (m), 1066 (m), 900 (w), 729 (m); LR-MS (pos. ESI, MeOH/CH_2Cl_2): *m/z* 534 $[M+Na]^+$, 520, 456; HR-MS (ESI, [u]): found: 534.089, calcd: 534.0892; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.55 (m, 2H, Ar), 7.46 (m, 1H, Ar), 7.37–7.24 (m, 4H, Ar), 7.23–7.16 (m, 2H, Ar), 6.38 (dd, 1H, 9.9/4.7 Hz, H-3), 6.29 (d, 1H, 4.6 Hz, H-5), 5.80 (d, 1H, 9.9 Hz, H-7), 3.84 and 3.82 (2 s, 6H, H-12, H-13), 3.45 (q*, 1H, 4.6 Hz, H-4), 2.21 (m, 1H, H-15), 1.20 and 0.85 (2d, 6H, 6.8 Hz, H-16, H-16′); ^{13}C-NMR (75 MHz, APT, $CDCl_3$): δ 167.6 and 167.0 (C-10 and C-11), 166.4 (C-8), 139.8, 137.8, 137.4, 136.9 (all C_{quart}), 133.5 (CH_{arom}), 133.1 (C_{quart}), 131.4, 129.7, 128.7, 128.3, 127.6, 126.6, 125.0 (all CH_{arom} and C-5), 119.1 (C_{quart}), 52.8 and 52.6 (C-12, C-13), 45.4 (C-3), 44.3 (C-4), 30.3 (C-15), 21.2 and 17.7 (C-16, C-16′).

Dimethyl 6-acetylamino-5-bromo-3-ethylcyclohexa-1,3-dien-1,2-dicarboxylate (14). Work-up: SiO_2, ea : ch 1 : 1; R_f 0.15; yellow oil; yield: 38%. IR (ATR): $1/\lambda$ [cm^{-1}] 3272 (br, s), 2952 (w), 1721 (s), 1666 (s), 1518 (m), 1433 (m), 1370 (m), 1250 (s), 1062 (m), 948 (w), 920 (w), 730 (w); LR-MS (pos. ESI, MeOH): *m/z* 383 $[M+Na]^+$, 381, 378, 333; HR-MS (ESI, [u]): found: 382.026 $[M+Na]^+$, calcd: 382.0266; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.21 (d, 1H, 4.4 Hz, H-5), 5.65 (dd, 1H, 9.7/5.1 Hz, H-3), 5.30 (d, 1H, 9.7 Hz, H-7), 3.79 and 3.75 (2 s, 6H, H-12, H-13), 3.31 (m, 1H, H-4), 2.03 (s, 3H, H-9), 1.76 (m, 1H, H-14), 1.61 (m*, 1H, 7.0 Hz, H-14′), 0.91 (t, 3H, 7.4 Hz, H-15); ^{13}C-NMR (75 MHz, APT, $CDCl_3$): δ 169.3 (C-8), 167.2 and 165.8 (C-10, C-11), 139.0 (C-1), 132.5 (C-5), 132.4 (C-2), 120.1 (C-6), 53.0 and 52.9 (C-12, C-13), 49.5 (C-3), 41.5 (C-4), 25.6 (C-14), 23.3 (C-9), 10.3 (C-15).

***N*-[2,6-Dimethyl-7-(3-methylbut-2-enyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl]-acetamide (23a).** Work-up: SiO_2, ea : ch 1 : 2; R_f 0.15; white solid; yield: 39% of two inseparable diastereomers (*syn* : *anti* (2 : 1) at C-6). Mp ~ 137 °C; IR (ATR): $1/\lambda$ [cm^{-1}] 3379 (br, w), 3286 (br, w), 2912 (w), 1767 (w), 1691 (s), 1517 (br, m), 1433 (m), 1379 (m), 1336 (w), 1285 (m), 1111 (m), 1030 (w), 992 (w); LR-MS: (EI, ethyl acetate): *m/z* 304 $[M]^+$, 260, 193, 177, 150, 107, 91, 69; HR-MS (EI, [u]): found: 304.178 $[M]^+$, calcd: 304.1787; ^{1}H-NMR (300 MHz, $CDCl_3$): major (*syn*) diastereomer, δ 7.18 (d, 1H, 8.2 Hz, H-7′), 5.37 (m, 1H, H-4), 5.19 (m, 1H, H-15), 4.57 (m, 1H, H-3), 3.15 (m, 2H, H-1, H-2), 2.90 (s, 3H, H-12), 2.75 and 2.51 (2 m, 2H, H-14), 2.35 (m, 1H, H-6), 2.07 (s, 3H, H-9), 1.73 and 1.71 (2 s, 6H, H-17, H-18), 1.58 (s, 3H, H-13); ^{13}C-NMR (75 MHz, APT, $CDCl_3$): *syn* : *anti* mixture: δ 179.2 and 177.4 (C-10, C-11), 170.1, 170.0 (C-8, C-8′), 140.5, 140.4 (C-16, C-16′), 134.4 (C-5), 133.2 (C-5′), 125.4 (C-4), 124.5 (C-4′), 122.4 (C-15), 121.3 (C-15′), 46.1, 44.2, 43.3, 42.5, 42.2, 42.1, 41.7, 40.0 (C-1, C-1′, C-2, C-2′, C-3, C-3′, C-6, C-6′), 30.3 (C-14′), 26.3 (C-14), 26.0 (C-13, C-13′), 25.2 (C-12′), 24.8 (C-12), 23.6 (C-9), 23.1 (C-9′), 19.2, 18.1 (C-17, C-17′, C-18, C-18′).

***N*-[5-Bromo-2,6-dimethyl-1,3-dioxo-2,3,3a,4,7,7a-hexa-hydro-1*H*-isoindol-4-yl]-acetamide (25).** Work-up: crude residue suspended in diethyl ether, then filtered, white solid; R_f (ea : ch 2 : 1) 0.15; yield: 71%. Mp 142 °C; IR (ATR): $1/\lambda$ [cm^{-1}] 3392 (w), 2944 (w), 1772 (w), 1691 (s), 1512 (m), 1434 (m), 1382 (m), 1321 (m), 1284 (m), 1130 (w), 1015 (w); LR-MS (EI, ethyl acetate): *m/z* 316 $[M]^+$, 273 $[M-CH_3CO]^+$, 235 $[M-Br]^+$, 186, 161, 124, 107; HR-MS (ESI, [u]): found: 337.016 $[M]^+$, calcd: 337.0164; ^{1}H-NMR (300 MHz, CD_2Cl_2): δ 7.26 (d, 1H, 8.4 Hz, H-7), 4.82 (m, 1H, H-3), 3.29 (dd, 1H, 8.9/5.6 Hz, H-2), 3.15 (dt, 1H, 7.2/1.6 Hz, H-1), 2.91 (s, 3H, H-12), 2.72 (dd, 1H, 15.3/1.6 Hz, H-6), 2.43 (dd, 1H, 15.3/7.1 Hz, H-6′), 2.09 (s, 3H, H-9), 1.85 (m, 3H, H-13); ^{13}C-NMR (75 MHz, APT, CD_2Cl_2): δ 178.5 and 178.2 (C-10, C-11), 170.1 (C-8), 134.8 (C-5), 118.5 (C-4), 48.4 (C-3), 43.5 (C-2), 39.0 (C-1), 31.8 (C-6), 25.3 (C-12), 23.9 (C-13), 23.5 (C-9).

4-*N*-(Benzyloxycarbonylamino)-2-methyl-5-phenyl-7-iso-propyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole (31). Work-up: precipitated from ea : ch 1 : 1, washed with cold Et_2O; colorless solid; yield: 83%. Mp 171 °C; IR (ATR): $1/\lambda$ [cm^{-1}] 3404 (w), 3029 (w), 2957 (w), 2868 (w), 1716 (s), 1687 (s), 1507 (s), 1435 (m), 1338 (m), 1330 (m), 1286 (m), 1230 (m), 1171 (w), 1117 (w), 1078 (m), 1057 (m), 1027 (m), 982 (w), 910 (m), 763 (s), 729 (s); LR-MS (pos. ESI, MeOH, CH_2Cl_2): *m/z* 455 $[M+Na]^+$, 389, 372, 282, 91; HR-MS (ESI, [u]): found: 455.195 $[M+Na]^+$, calcd: 455.1947; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.35–7.24 (m, 8H, Ph), 6.99 (m, 2H, Ph), 6.35 (d, 1H, 9.9 Hz, H-7), 5.79 (m, 1H, H-5), 5.15 and 5.01 (2d, 2H, 12.2 Hz, H-9), 4.57 (m, 1H, H-3), 3.44 (dd, 1H, 8.5/6.0 Hz, H-2), 3.35 (dd, 1H, 8.5/5.7 Hz, H-1), 2.96 (s, 3H, H-13), 2.24 (m, 1H, H-15), 2.04 (m, 1H, H-6), 1.24 and 1.06 (2d, 6H, 6.3 Hz, H-16, H-16′); ^{13}C-NMR (75 MHz, APT, $CDCl_3$): δ 178.8 and 177.0 (C-10, C-11), 156.1 (C-8), 143.0 (C-10), 137.6 (C_{quart}), 136.6 (C-4), 129.7–127.6 (10 CH_{arom}, C-5), 66.9 (C-9), 50.1 (C-3), 45.0 (C-2), 44.8 (C-6), 41.4 (C-1), 28.4 (C-14), 24.9 (C-12), 22.3 and 21.3 (C-15, C-15′).

***N*-(2,4-Dimethyl-6-nitro-5-phenylcyclohex-2-enyl)-acetamide (36).** Work-up: suspended in diethyl ether, filtration; white solid; R_f 0.21 (ea : ch 1 : 1); yield: 79%. Mp 203 °C; IR (ATR): $1/\lambda$ [cm^{-1}] 3271 (w), 2970 (w), 1733 (m), 1653 (s), 1550 (s), 1454 (m), 1371 (s), 1241 (s), 1042 (m), 913 (w), 725 (m); LR-MS (pos. ESI, MeOH/CH_2Cl_2): *m/z* 289 $[M+H]^+$, 242 $[M-NO_2]^+$, 200, 183, 157; HR-MS (ESI, [u]): found: 289.154 $[M+H]^+$, calcd: 289.1552; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.26-7.19 (m, 5H, Ph), 5.64 (d, 1H, 9.6 Hz, H-7), 5.52 (s, 1H, H-5), 5.26 (m, 1H, H-3), 5.22 (dd, 1H, 12.3/4.9 Hz, H-2), 2.81 (dd, 1H, 12.3/10.3 Hz, H-1), 2.36 (m, 1H, H-6), 2.02 (s, 3H, H-9), 1.80 (s, 3H, H-10), 0.91 (d, 3H, 6.9 Hz, H-11); ^{13}C-NMR (75 MHz, APT, $CDCl_3$): δ 170.3 (C-8), 138.9 (C-12), 131.5 (C-5), 130.3 (C-4), 128.9, 128.0, 127.7 (5C, Ph), 89.0 (C-2), 49.3 (C-3), 46.7 (C-1), 38.1 (C-6), 23.2 (C-9), 20.6 (C-10), 19.5 (C-11).

General procedure for the aromatization of aminocyclohexadienes and aminocyclohexenes

The cycloadduct (1 equiv.), MnO_2 (85%, 3–10 equiv.) and toluene (~5–10 mL $mmol^{-1}$) were combined in a reaction tube. The tube was sealed with a septum and the reaction stirred at 110 °C in an oil bath. After 5–48 h, the solvent and other volatile compounds were removed by oil pump vacuum. Silica gel flash chromatography (ethyl acetate : cyclohexane) gave the aromatic product in analytically pure form.

Dimethyl 3-benzylamino-4,6-diphenylphthalate (42). Work-up: SiO_2, ea : ch 1 : 1; R_f 0.55; yellow solid; yield: 65%. Mp 203 °C; IR (ATR): $1/\lambda$ [cm^{-1}] 3302 (w), 3025 (w), 2947 (w), 2245 (w), 1726

(s), 1652 (m), 1508 (m), 1480 (s), 1432 (m), 1343 (m), 1287 (s), 1232 (s), 1132 (w), 1068 (m), 905 (m), 728 (s); LR-MS (pos. ESI, MeOH/CH_2Cl_2) *m/z* 488 $[M+Na]^+$, 434, 402, 367; HR-MS (ESI, [u]): found: 488.147 $[M+Na]^+$, calcd: 488.1474; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.51 (s, 1H, H-7), 7.67 (m, 2H, Ph), 7.50–7.28 (m, 14H, Ph), 3.83 and 3.61 (2 s, 6H, H-12, H-13); ^{13}C-NMR (75 MHz, APT, $CDCl_3$): δ 168.7 and 167.1 (C-10, C-11), 140.8, 140.7, 139.8, 139.4, 138.9, 138.5, 134.1, 132.5 (8 C_{quart}), 129.0–127.2 (16 CH_{arom}), 53.2 and 52.5 (C-12, C-13), C-8 obscured.

Dimethyl 3-(2-bromobenzamido)-4-phenyl-6-isopropyl-phthalate (45). Work-up: SiO_2, ea : ch 2 : 1, R_f 0.43; yellow solid; yield: 86%. Mp 160 °C; IR (ATR): $1/\lambda$ [cm^{-1}] 3300 (br, w), 2953 (w), 1730 (s), 1670 (m), 1593 (w), 1493 (m), 1430 (m), 1320 (m), 1266 (m), 1206 (s), 1103 (m), 1020 (w), 903 (w), 726 (m); LR-MS (pos. ESI, MeOH): *m/z* 532 $[M+Na]^+$, 478, 430, 249, 234; HR-MS (ESI, [u]): found: 532.073 $[M+Na]^+$, calcd: 532.0736; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H, H-7), 7.52–7.25 (m, 10H, Ph), 3.91 and 3.86 (2 s, 6H, H-12, H-13), 3.17 (sept, 1H, 6.8 Hz, H-15), 1.20 (d, 6H, 6.8 Hz, H-16, H-16′); ^{13}C-NMR (75 MHz, APT, $CDCl_3$): δ 168.5 and 167.2 (C-10, C-11), 165.8 (C-8), 145.6, 141.6, 140.0, 138.8, 137.4 (C_{quart}), 133.6 (CH_{arom}), 132.2 (C_{quart}), 131.6, 130.9 (CH_{arom}), 130.0 (C_{quart}), 129.2, 129.1, 128.8, 128.5, 128.4, 128.2 (all CH_{arom}), 128.1 (C_{quart}), 127.0 (CH_{arom}), 53.1 and 52.6 (C-12, C-13), 30.7 (C-15), 24.0 (C-16, C-16′).

Dimethyl 3-acetylamino-4-bromo-6-ethylphthalate (49). Work-up: SiO_2, ea : ch 2 : 1; R_f 0.32; yellow oil; yield: 70%. IR (ATR): $1/\lambda$ [cm^{-1}] 3260 (w), 2953 (w), 1731 (s), 1680 (m), 1570 (w), 1434 (m), 1278 (m), 1203 (m), 1123 (m), 1030 (w), 960 (w), 923 (w), 880 (w); LR-MS (EI, ethyl acetate): *m/z* 358 $[M]^+$, 342 $[M–CH_3]^+$, 326 $[M–CH_3CH_2]^+$, 278, 246, 199, 159; HR-MS (ESI, [u]): found: 380.010 $[M+Na]^+$, calcd: 380.0110; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.62 (s, 1H, H-5), 7.52 (s, 1H, H-7), 3.87 and 3.83 (2 s, 6H, H-12, H-13), 2.65 (q, 2H, 7.5 Hz, H-14), 2.18 (s, 3H, H-9), 1.23 (t, 3H, 7.5 Hz, H-15); ^{13}C-NMR (75 MHz, APT, $CDCl_3$): δ 168.6 (C-8), 167.8 and 166.3 (C-10, C-11), 141.9 (C-6), 135.7 (C-5), 132.4 (C-1), 131.8 (C-3), 129.4 (C-2), 123.3 (C-4), 53.0 and 52.7 (C-12, C-13), 26.5 (C-14), 23.7 (C-9), 15.4 (C-15).

***N*-[2,6-Dimethyl-7-(3-methylbut-2-enyl)-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]-acetamide (54).** Work-up: SiO_2, ea : ch 1 : 1; R_f 0.58; white solid; yield: 71%. Mp 143 °C; IR (ATR): $1/\lambda$ [cm^{-1}] 3326 (w), 2920 (w), 1692 (s), 1610 (m), 1513 (m), 1436 (m), 1376 (m), 1236 (m), 1046 (w), 993 (w); LR-MS (EI, ethyl acetate): *m/z* 300 $[M]^+$, 285 $[M–CH_3]^+$, 245, 228, 203, 186, 172, 258, 143, 128; HR-MS (EI, [u]): found: 300.147 $[M]^+$, calcd: 300.1474; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.50 (s, 1H, H-7), 8.53 (s, 1H, H-4), 4.97 (t, 1H, 6.8 Hz, H-15), 3.78 (d, 2H, 6.8 Hz, H-14), 3.12 (s, 3H, H-12), 2.39 (s, 3H, H-13), 2.24 (s, 3H, H-9), 1.80 (s, 3H, H-17), 1.68 (s, 3H, H-18); ^{13}C-NMR (75 MHz, APT, $CDCl_3$): δ 169.5 and 169.4 (C-10, C-11), 169.1 (C-8), 147.4 (C-6), 135.4 (C-5), 133.3 (C-16), 126.0 (C-4), 120.9 (C-15), 114.1 (C-3), 26.7 (C-14), 25.9 (C-18), 25.1 (C-9), 23.7 (C-12), 20.3 (C-13), 18.2 (C-17), C-1 and C-2 obscured.

***N*-(5-Bromo-2,7-dimethyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)-acetamide (55).** Work-up: SiO_2, ea : ch 2 : 1, R_f 0.35; white solid; yield: 68%. Mp 234 °C; IR (ATR): $1/\lambda$ [cm^{-1}] 3226 (w), 3181 (w), 2923 (w), 1766 (m), 1703 (s), 1677 (s), 1518 (m), 1433 (m), 1378 (m), 1259 (m), 1099 (w), 1014 (m), 903 (w); LR-MS (EI, ethyl acetate): *m/z* 311 $[M]^+$, 295 $[M–CH_3]^+$, 269 $[M–Ac]^+$, 253 $[M–AcNH]^+$, 231 $[M–Br]^+$, 211, 189, 145; HR-MS (ESI, [u]): found: 332.984 $[M+Na]^+$, calcd: 332.9845; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.72 (s, 1H, H-5), 7.56 (s, 1H, H-7), 3.12 (s, 3H, H-12), 2.64 (s, 3H, H-13), 2.28 (s, 3H, H-9); ^{13}C-NMR (125 MHz, APT, $CDCl_3$): δ 168.8 (C-8), 167.9 and 166.8 (C-10, C-11), 140.8 (C-5), 137.0 (C-1), 131.1 (C-2), 128.6 (C-6), 127.0 (C-4), 126.6 (C-3), 24.0 (C-12), 23.7 (C-9), 17.2 (C-13).

***N*-(3-Cyano-5-isopropylbiphenyl-2-yl)acetamide (63).** Work-up: SiO_2, ea : ch 1 : 1; R_f 0.41; yellow oil; yield: 75%. IR (ATR): $1/\lambda$ [cm^{-1}] 3235 (w), 2960 (w), 1664 (s), 1593 (w), 1499 (m), 1367 (w), 1286 (w), 1007 (w); LR-MS (EI, ethyl acetate): *m/z* 278 $[M]^+$, 236 $[M–Ac]^+$, 221 $[M–AcNH]^+$, 206, 192, 165; HR-MS (EI, [u]): found: 278.142 $[M]^+$, calcd: 278.1419; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.54–7.30 (m, 7H, Ph), 6.98 (s, 1H, H-7), 2.97 (sept, 1H, 6.9 Hz, H-10), 2.06 (s, 3H, H-9), 1.28 (d, 6H, 6.9 Hz, H-11, H-11′); ^{13}C-NMR (75 MHz, APT, $CDCl_3$): δ 169.2 (C-8), 148.7 (C-6), 140.1,

Table 7 Crystal structure data for compounds **24**, **36** and **46**

Compound reference	**24**	**36**	**46**
Chemical formula	$C_{12}H_{15}BrN_2O_3$	$C_{16}H_{20}N_2O_3$	$C_{26}H_{25}NO_5$
Formula Mass	315.17	288.34	431.47
Crystal system	Monoclinic	Monoclinic	Monoclinic
a/Å	10.8021(12)	11.9261(5)	14.6003(6)
b/Å	10.5357(7)	17.9405(14)	17.4066(8)
c/Å	13.5435(12)	15.2365(11)	9.8449(3)
α (°)	90.00	90.00	90.00
β (°)	124.200(6)	96.061(4)	115.519(2)
γ (°)	90.00	90.00	90.00
Unit cell volume/Å^3	1274.8(2)	3241.8(4)	2257.91(16)
T/K	100(2)	100(2)	100(2)
Space group	P21/c	P21/n	Cc
No. of formula units per unit cell, *Z*	4	8	4
No. of reflections measured	6562	15 743	4577
No. of independent reflections	2769	7009	2478
R_{int}	0.0445	0.0484	0.0237
Final R_1 values ($I > 2\sigma(I)$)	0.0372	0.0504	0.0334
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.0777	0.0984	0.0713
Final R_1 values (all data)	0.0608	0.1160	0.0450
Final $wR(F^2)$ values (all data)	0.0840	0.1154	0.0749

137.7, 134.2 (3 C_{quart}), 133.4–128.4 (7 CH_{arom}), 117.2 (C-12), 113.0 (C-1), 33.7 (C-10), 23.8 (C-11, C-11′), 23.3 (C-9).

***N*-(4,6-Dimethyl-2-nitrobiphenyl-3-yl)acetamide (64).** Work-up: SiO_2, ea : ch 1 : 1; R_f 0.56; yellow oil; yield: 75%. IR (ATR): $1/\lambda$ [cm^{-1}] 2920 (m), 2860 (w), 1720 (w), 1607 (m), 1486 (m), 1441 (m), 1383 (m), 1250 (m), 1223 (s), 1061 (s), 926 (m), 759 (s), 700 (s); LR-MS (ESI, MeOH): *m/z* 238 $[M–NO_2]^+$, 223 $[M–NO_2–CH_3]^+$, 213, 186, 137, 129, 105; ^{1}H-NMR (500 MHz, MeOD-d_4): δ 7.46–7.35 (m, 5H, Ph), 7.08 (s, 1H, H-5), 2.54 (s, 3H, H-9), 2.52 and 2.27 (2 s, 6H, H-10, H-11), H-7 obscured; ^{13}C-NMR (125 MHz, APT, MeOD-d_4): δ 165.1 (C-8), 150.5 (C-2), 138.9, 136.4 and 133.5 (3 C_{quart}), 131.0 and 129.4 (CH_{arom}), 128.7 (C_{quart}), 128.6 and 128.5 (CH_{arom}), 123.7 (C_{quart}), 19.8 (C-9), 16.3 and 14.1 (C-10, C-11).

Acknowledgements

This work was financed by the 7th European framework program (Cataflu. Or). We thank Prof. H.-G. Schmalz for excellent technical support.

Notes and references

1 (*a*) A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168–3210; (*b*) H. Bienaymé, C. Hulme, G. Oddon and P. Schmitt, *Chem.–Eur. J.*, 2000, **6**, 3321–3329; (*c*) J. Zhu and H. Bienaymé (ed.), *Multicomponent Reactions*, Wiley-VCH, Weinheim, 1st ed., 2005; (*d*) R. V. A. Orru and M. de Greef, *Synthesis*, 2003, 1471–1499; (*e*) A. Jacobi von Wangelin, H. Neumann, D. Gördes, S. Klaus, D. Strübing and M. Beller, *Chem.–Eur. J.*, 2003, **9**, 4286–4294.

2 (*a*) K. C. Nicolaou, S. A. Snyder, T. Montagnon and G. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2002, **41**, 1668–1698; (*b*) W. R. Roush, in *Comprehensive Organic Synthesis*, Vol. 5 (Ed.: B. M. Trost), Pergamon Press, New York, 1991, p. 513; (*c*) W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, New York, 1990 (Tetrahedron Organic Chemistry Series Vol. 8).

3 Sequential Diels–Alder and oxidation reactions: (*a*) S. Mekidechea and L. Désaubry, *Tetrahedron Lett.*, 2008, **49**, 5268–5270; (*b*) J. T. Vessels, S. Z. Janicki and P. A. Petillo, *Org. Lett.*, 2000, **2**, 73–76; (*c*) G. Hilt and K. I. Smolko, *Angew. Chem., Int. Ed.*, 2003, **42**, 2795–2797; (*d*) G. Hilt and M. Danz, *Synthesis*, 2008, (14), 2257–2263; (*e*) G. Hilt, S. Lüers and K. I. Smolko, *Org. Lett.*, 2005, **7**, 251–253; Acid-mediated aromatizations: (*f*) O. Diels and K. Alder, *Ber. Dtsch. Chem. Ges. B*, 1929, **62**, 554–562; (*g*) Y. Kitahara, T. Kato, N. Ototani, A. Inoue and H. Izumi, *J. Chem. Soc. C*, 1968, 2508–2510; (*h*) A. B. Smith and N. J. Liverton, *J. Am. Chem. Soc.*, 1986, **108**, 3040–3048; (*i*) K. Y. Jung and M. Koreeda, *J. Org. Chem.*, 1989, **54**, 5667–5675; (*j*) F. I. Zubkov and E. V. Boltukhina, *Tetrahedron*, 2004, **60**, 8455–8463; Base-mediated aromatizations: (*k*) A. P. Kozikowski and M. P. Kuniak, *J. Org. Chem.*, 1978, **43**, 2083–2084; (*l*) H. Hart and G. Nwokogu, *J. Org. Chem.*, 1981, **46**, 1251–1255; (*m*) Y. D. Xing and N. Z. Huang, *J. Org. Chem.*, 1982, **47**, 140–142; (*n*) D. H. Blank and G. W. Gribble, *Tetrahedron Lett.*, 1997, **38**, 4761–4764; (*o*) H. N. C. Wong, *Acc. Chem. Res.*, 1989, **22**, 145–152.

4 For a detailed overview of the multifaceted chemistry of anthranilic acid derivatives, see: (*a*) P. Wiklund, *Dissertation*, 2004, Karolinska University, ISBN: 91-7349-913-7; Selected recent examples: (*b*) P. Wiklund and J. Bergman, *Curr. Org. Synth.*, 2006, **3**, 379–402; (*c*) P. Karthikeyan, R. V. Jagadeesh, Y. S. Sandhya, Puttaswamy, P. Nithya, S. S. Kumar and P. R. Bhagat, *Appl. Organomet. Chem.*, 2011, **25**, 34–46.

5 (*a*) H. Neumann, A. Jacobi von Wangelin, D. Gördes, A. Spannenberg and M. Beller, *J. Am. Chem. Soc.*, 2001, **123**, 8398–8399; (*b*) A. Jacobi von Wangelin, H. Neumann, D. Gördes, A. Spannenberg and M. Beller, *Org. Lett.*, 2001, **3**, 2895–2898; (*c*) H. Neumann, A. Jacobi von Wangelin, D. Gördes, A. Spannenberg, W. Baumann and M. Beller, *Tetrahedron*, 2002, **58**, 2381–2387; (*d*) S. Klaus, S. Hübner, H. Neumann, D. Strübing, A. Jacobi von Wangelin, D. Gördes and M. Beller, *Adv. Synth. Catal.*, 2004, **346**, 970–978.

6 (*a*) D. Gördes, A. Jacobi von Wangelin, S. Klaus, H. Neumann, D. Strübing, S. Hübner, H. Jiao, W. Baumann and M. Beller, *Org. Biomol. Chem.*, 2004, **2**, 845–851; (*b*) A retro-Diels–Alder reaction of the cycloadduct could not be accomplished. The aminodiene intermediate, however, undergoes partial retro-condensation when water is present.

7 Somatostatin analogues: (*a*) M. Sukopp, R. Schwab, L. Marinelli, E. Biron, M. Heller, E. Varkondi, A. Pap, E. Novellino, G. Keri and H. Kessler, *J. Med. Chem.*, 2005, **48**, 2916–2926; Bicyclo[2.2.2]-octenes: (*b*) D. Strübing, A. Jacobi von Wangelin, H. Neumann, D. Gördes, S. Hübner, S. Klaus, A. Spannenberg and M. Beller, *Eur. J. Org. Chem.*, 2005, 107–113; Luminols: (*c*) H. Neumann, S. Klaus, M. Klawonn, D. Strübing, S. Hübner, D. Gördes, A. Jacobi von Wangelin, M. Lalk and M. Beller, *Z. Naturforsch.*, 2004, **59b**, 431–438; Aza-Corollosporin analogues: (*d*) H. Neumann, D. Strübing, M. Lalk, S. Klaus, S. Hübner, A. Spannenberg, U. Lindequist and M. Beller, *Org. Biomol. Chem.*, 2006, **4**, 1365–1375; Phenanthridones: (*e*) A. Jacobi von Wangelin, H. Neumann, D. Gördes, S. Hübner, C. Wendler, S. Klaus, D. Strübing, A. Spannenberg, H. Jiao, L. El Firdoussi, K. Thurow, N. Stoll and M. Beller, *Synthesis*, 2005, 2029–2038.

8 The yield of the cycloadducts showed a strong dependence on the pK_a of the employed acid catalyst: *p*-TSA·H_2O (pK_a –2.8) had equal activity as water-free TSA; camphorsulfonic acid (pK_a 1.2), *ortho*-phosphoric acid (2.1), and other Lewis acids gave much lower conversion under otherwise identical conditions. For more details, see also: R. Fichtler, *Dissertation*, University of Cologne, 2011.

9 Examples of amide–aldehyde condensations and subsequent reactions of *N*-acylimines and *N*-acyliminium ions: (*a*) W. A. Noyes and D. B. Forman, *J. Am. Chem. Soc.*, 1933, **55**, 3493–3494; (*b*) A. M. Kraft and R. M. Herbst, *J. Org. Chem.*, 1945, **10**, 483–497; (*c*) A. Couture, R. Dubiez and A. Lablache-Combier, *J. Org. Chem.*, 1984, **49**, 714–717; (*d*) H. E. Zaugg, *Synthesis*, 1984, 181–212; (*e*) A. R. Katritzky, A. V. Ignatchenko and H. Lang, *Synth. Commun.*, 1995, **25**, 1197–1204; (*f*) C. M. Marson and A. Fallah, *Chem. Commun.*, 1998, 83–84; (*g*) A. Guirado, R. Andreu, A. Cerezo and J. Gálvez, *Tetrahedron*, 2001, **57**, 4925–4931; (*h*) C. M. Marson, *Arkivoc*, 2001, (i), 1–16; (*i*) J. Elaridi, A. Thaqi, A. Prosser, W. R. Jackson and A. J. Robinson, *Tetrahedron: Asymmetry*, 2005, **16**, 1309–1319; (*j*) M. Lei, L. Ma and L. Hu, *Tetrahedron Lett.*, 2010, **51**, 4746–4749.

10 A. Jacobi von Wangelin, H. Neumann, D. Gördes, S. Klaus, H. Jiao, A. Spannenberg, T. Krüger, C. Wendler, K. Thurow, N. Stoll and M. Beller, *Chem.–Eur. J.*, 2003, **9**, 2273–2281.

11 1,4-Cyclohexadiene isomers have been isolated from similar reactions with 2-pentenal and 2-hexenal: D. Strübing, H. Neumann, A. Jacobi von Wangelin, S. Klaus, S. Hübner and M. Beller, *Tetrahedron*, 2006, **62**, 10962–10967.

12 Aldehydes for the synthesis of **17** and **18** were prepared *via* a Peterson olefination according to: E. J. Corey, D. Enders and M. G. Bock, *Tetrahedron Lett.*, 1976, **17**, 7–10.

13 (*a*) For computational studies on the reaction mechanism, see the Supporting Information of ref. 5*a*; Diastereoselective reactions with (S)-methyl pyroglutamate: (*b*) S. Hübner, D. Michalik, H. Jiao, H. Neumann, S. Klaus, D. Strübing, A. Spannenberg and M. Beller, *Chem.–Asian J.*, 2007, **2**, 734–746.

14 For identity and analytical data of regioisomer **23b** containing a methylpentenyl side chain in 5-position, see ESI†.

15 2-Bromocrotonaldehydes were prepared from the aldehyde and aqueous bromine in the presence of triethylamine: (*a*) C. J. Kowalski, A. E. Weber and K. W. Fields, *J. Org. Chem.*, 1982, **47**, 5088–5093; (*b*) H. Lütjens and P. Knochel, *Tetrahedron: Asymmetry*, 1994, **5**, 1161–1162.

16 (*a*) B. Potthoff and E. Breitmeier, *Chem. Ber.*, 1987, **120**, 255–257; (*b*) G. Bobowski, B. West and D. Omecinsky, *J. Heterocycl. Chem.*, 1992, **29**, 33–49; (*c*) J. Barluenga, F. Aznar and M. Fernández, *Tetrahedron Lett.*, 1995, **36**, 6551–6554; (*d*) K. Bogdanowicz-Szwed and A. Budzowski, *Monatsh. Chem.*, 2001, **132**, 947–957; (*e*) A. K. Weber and A. Jacobi von Wangelin, manuscript in preparation.

17 Acetoxydienes in related reactions: (*a*) D. Strübing, A. Kirschner, H. Neumann, S. Hübner, S. Klaus, U. T. Bornscheuer and M. Beller, *Chem.–Eur. J.*, 2005, **11**, 4210–4218; Other oxadienes in Diels–Alder reactions: (*b*) R. C. Cookson, M. C. Cramp and P. J. Parsons, *J. Chem. Soc., Chem. Commun.*, 1980, 197–198; (*c*) J. Becher, H. C. Nielsen, J. P. Jacobsen, O. Simonsen and H. Clausen, *J. Org. Chem.*, 1988, **53**, 1862–1871; (*d*) C. J. Suckling, M. C. Tedford, L. M. Bence, J. I. Irvine and W. H. Stimson, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 49–52.

18 (*a*) Z. Rappoport, (Ed.), *The Chemistry of Anilines, Part 1*, Wiley, 2007; Selected examples of aniline syntheses: (*b*) A. Padwa, M. Dimitroff, A. G. Waterson and T. Wu, *J. Org. Chem.*, 1997, **62**, 4088–4096; N.

Xia and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 337–339; F. Lang, D. Zewge, I. N. Houpis and R. P. Volante, *Tetrahedron Lett.*, 2001, **42**, 3251–3254; A. H. Stoll and P. Knochel, *Org. Lett.*, 2008, **10**, 113–116; (*c*) Selected pharmaceuticals containing an anilide structure: Acebutolol, Bicalutamide, Etidocaine, Flutamide, Ivacaftor, Levobupivacaine, Mepivacaine, Platensimycin; (*d*) Selected radiocontrast agents: Adipiodone, Iodoxamic acid, Iotrolan, Tyropanoic acid; (*e*) Selected aniline dyes and stains: Coomassie brilliant blue, Janus green B, Patent blue V, Bismarck brown Y; For biologically active anilides, see for example: (*f*) B. Narasimhan, R. Narang, V. Judge, R. Ohlan and S. Ohlan, *Arkivoc*, 2007, (xv), 112–126; G. Bouchain and D. Delorme, *Curr. Med. Chem.*, 2003, **10**, 2359–2372; P. Wiklund and J. Bergman, *Tetrahedron Lett.*, 2004, **45**, 969–972; M. Gohbara, S. O. Duke and T. Takematsu, *Agric. Biol. Chem.*, 1988, **52**, 465–472; For aniline polymers, see: (*g*) Y. Wang, H. D. Tran and R. B. Kaner, *Macromol. Rapid Commun.*, 2011, **32**, 35–49.

19 (*a*) For aromatizations with DDQ, see refs 3*b–d*; aromatization with oxygen: (*b*) T. Moriuchi, K. Kikushima, T. Kajikawa and T. Hirao, *Tetrahedron Lett.*, 2009, **50**, 7385–7387; (*c*) H. Tanaka, T. Ikeno and T. Yamada, *Synlett*, 2003, 576–578; (*d*) N. Nakamichi, H. Kawabata and M. Hayashi, *J. Org. Chem.*, 2003, **68**, 8272–8273; Pd catalysts: (*e*) C. A. Busacca and Y. Dong, *Synth. Commun.*, 2000, **30**, 501–509; (*f*) J. Cossy and D. Belotti, *Org. Lett.*, 2002, **4**, 2557–2559; (*g*) M. Hayashi, K. Yamada and S. Nakayama, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1501–1503; (*h*) For more examples, see also: J. March, *Advanced Organic Chemistry*, 4th ed., Wiley, New York, 1992, pp 1162.

20 MnO_2-mediated oxidations of related systems: (*a*) J. C. Leffingwell and H. J. Bluhm, *J. Chem. Soc. D*, 1969, 1151–1152; (*b*) W. Oppolzer, L. Bieber and E. Francotte, *Tetrahedron Lett.*, 1979, **20**, 4537–4540; For other MnO2-mediated oxidation reactions of (hetero)arenes, see for example: (*c*) A. T. Soldatenkov, K. B. Polyanskii, N. M. Kolyadina and S. A. Soldatova, *Chem. Heterocycl. Compd.*, 2009, **45**, 633–657; (*d*) F. Delgado, C. Alvarez, O. Garcia, G. Pernieres and C. Marquez, *Synth. Commun.*, 1991, **21**, 2137–2141; (*e*) A. J. Fatiadi, *Synthesis*, 1976, 65–104; (*f*) A. J. Fatiadi, *Synthesis*, 1976, 133–167.

21 (*a*) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.*, 1952, 1094–1111; (*b*) I. M. Goldman, *J. Org. Chem.*, 1969, **34**, 1979–1981.

22 Anilides serve as test systems for the development of metal-catalyzed CH functionalization reactions. For recent examples, see: (*a*) H. Liu, X. Wang and Y. Gu, *Org. Biomol. Chem.*, 2011, **9**, 1614–1620; (*b*) K. Sun, Y. Li, T. Xiong, J. Zhang and Q. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 1694–1697; (*c*) R. B. Bedford, J. U. Engelhart, M. F. Haddow, C. J. Mitchell and R. L. Webster, *Dalton Trans.*, 2010, **39**, 10464–10472; (*d*) C. S. Yeung, X. Zhao, N. Borduas and V. M. Dong, *Chem. Sci.*, 2010, **1**, 331–336; (*e*) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 16474–16475.

23 R. Pérez-Ruiz, R. Fichtler, Y. Diaz Miara, M. Nicoul, D. Schaniel, H. Neumann, M. Beller, D. Blunk, A. G. Griesbeck and A. Jacobi von Wangelin, *J. Fluoresc.*, 2010, **20**, 657–664.

24 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2008, **64**, 112–122.

