Coupling–isomerization–Claisen sequences – mechanistic dichotomies in hetero domino reactions†‡

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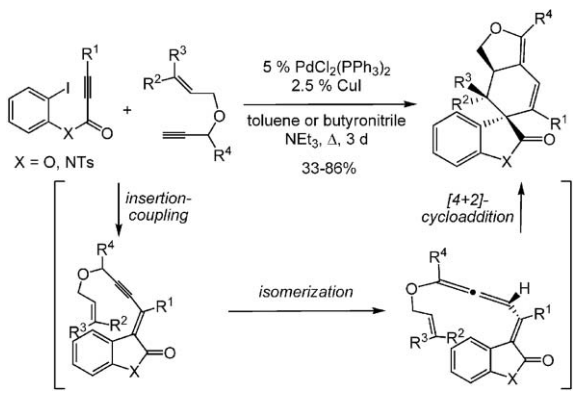
A new coupling–isomerization–Claisen domino reaction starting from electron deficient halides and 1-(hetero)aryl propargyl trityl ethers dichotomizes in the concluding steps of the sequence and gives rise to the formation of tricyclo[3.2.1.0^{2,7}]oct-3-enes, enones, 1*H*-isochromenes, or indans as a consequence of minute differences of substituent effects.

The coupling–isomerization reaction[1] (CIR) of electron deficient (hetero)aryl halides and (hetero)aryl propargyl alcohols under the conditions of the Sonogashira coupling[2] is a domino process[3] and furnishes 1,3-di(hetero)aryl propenones in good yields. In recent years, this new chalcone synthesis has been elaborated into an entry to consecutive one-pot syntheses of pharmaceutically relevant heterocycles.[1,4] Mechanistically, the CIR proceeds as a rapid palladium–copper catalyzed alkyne coupling followed by a rate determining base catalyzed propargyl alcohol to enone isomerization. Addressing the *in situ* generation of allenyl species we have discovered a new hetero domino reaction based upon a CI–Diels–Alder sequence *via* a vinyl allenyl allyl ether intermediate that gives rise to the formation of spirocyclic benzofuranones and indolones (Scheme 1).[5]

Encouraged by this intriguing hetero domino reaction, the kinetic stabilization of an allenyl intermediate by a bulky propargyl



Scheme 1 CIR–Diels–Alder sequence to spirocyclic benzofuranones and indolones.

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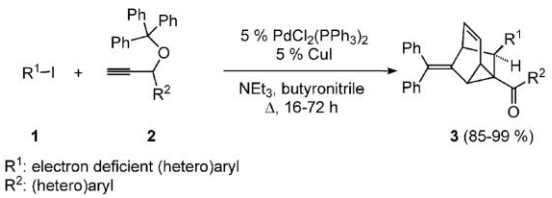
† Electronic supplementary information (ESI) available: Experimental procedures and characterization for compounds **3**, **4**, **6** and **7**. See DOI: 10.1039/b609669g

‡ This work is dedicated to Prof. Dr. Dr. h.c. Rolf Gleiter on the occasion of his 70th birthday.



Scheme 2

ether substituent was conceived and should open new reactivity profiles for the development of Pd-catalyzed sequential and domino reactions.[6] Here, we report a series of CI–pericyclic sequences and their mechanistic dichotomies with propargyl trityl ethers as substrates.

Initial attempts to isolate the proposed allenyl intermediates of CIR as allenyl methyl or silyl ethers always led to the formation of complex mixtures of cyclobutane stereoisomers arising from [2 + 2]-cycloadditions. With the support of molecular modelling studies trityl ethers were identified to shield the cumulated double bonds of the generated allene most effectively from dimerizations.

However, upon submitting a whole series of electron deficient (hetero)aryl halides **1** and (hetero)aryl propargyl trityl ethers **2** to the conditions of the CIR, *i.e.* in a boiling 1 : 1 mixture of butyronitrile and triethylamine and in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI, tricyclo[3.2.1.0^{2,7}]oct-3-enes **3**§¶ are isolated in excellent yields (Scheme 2, Table 1). In this process four new carbon–carbon bonds and a complex tricyclic framework are formed with high efficiency.

The structures of tricyclo[3.2.1.0^{2,7}]oct-3-enes **3** were unambiguously supported by spectroscopic (^{1}H, ^{13}C and DEPT, COSY,

Table 1 Coupling–isomerization–Claisen rearrangement–Diels–Alder domino sequence to tricyclo[3.2.1.0^{2,7}]oct-3-enes **3**[a]

Entry	Tricyclo[3.2.1.0^{2,7}]oct-3-ene **3** (yield)[b]
1	**3a** (R^1 = 2-thiazolyl, R^2 = Ph, 85%)
2	**3b** (R^1 = *p*-$O_2NC_6H_4$, R^2 = Ph, 91%)
3	**3c** (R^1 = *p*-$F_3CC_6H_4$, R^2 = Ph, 97%)
4	**3d** (R^1 = *p*-$F_3CC_6H_4$, R^2 = *p*-anisyl, 98%)
5	**3e** (R^1 = *p*-$F_3CC_6H_4$, R^2 = *p*-tolyl, 99%)
6	**3f** (R^1 = *p*-$F_3CC_6H_4$, R^2 = *p*-ClC_6H_4, 99%)
7	**3g** (R^1 = *p*-$MeO_2CC_6H_4$, R^2 = 2-thienyl, 92%)
8	**3h** (R^1 = *p*-NCC_6H_4, R^2 = 2-thienyl, 89%)

[a] Reaction conditions: 1.0 equiv. of the (hetero) aryl iodide **1**, 1.1 equiv. of propargyl trityl ether **2** (0.1 M in butyronitrile–triethylamine 1 : 1), 0.05 equiv. of $PdCl_2(PPh_3)_2$ and 0.05 equiv. of CuI were heated to reflux temp. for 16–72 h. [b] Yields refer to isolated yields of tricyclo[3.2.1.0^{2,7}]oct-3-enes **3** after flash chromatography on silica gel and crystallization to be ⩾ 95% pure as determined by NMR spectroscopy and elemental analysis.

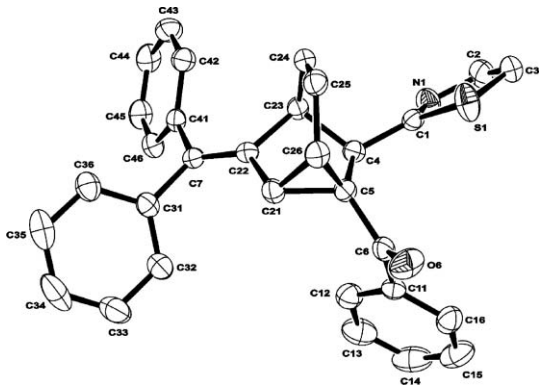
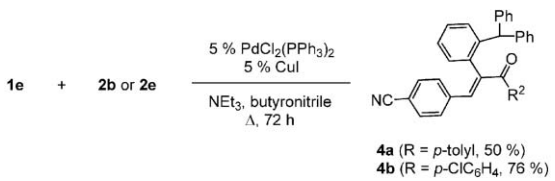


Fig. 1 Molecular structure of tricyclo[3.2.1.$0^{2,7}$]oct-3-ene **3a** (protons were omitted for clarity, ORTEP: 50% probability).

NOESY, HETCOR and HMBC NMR experiments, IR, UV/Vis, mass spectrometry) and combustion analyses. Additionally, the molecular structure was corroborated by an X-ray structure analysis of compound **3a** (Fig. 1).‖

With respect to the substitution pattern of the (hetero)aryl halides **1** and (hetero)aryl propargyl trityl ethers **2** the domino process appears to be quite general. However, upon reacting *para*-cyanobenzonitrile (**1e**) with slightly electron rich (**2b**) or slightly electron poor propargyl trityl ethers (**2e**) a completely different outcome of the sequence is observed and the enones **4** are obtained in moderate to good yields (Scheme 3).¶ Again, the molecular structure was unambiguously supported by an X-ray structure analysis of compound **4b** (Fig. 2).‖

Obviously, this puzzling result is caused by minute electronic substituent effects of the aryl halide and the propargyl trityl ether. Hence, even stronger electron withdrawing groups, such as carbonyl groups, directly linked to the isomerizing propargyl trityl ether moiety should enhance the rate of the concluding pericyclic step. Therefore, (hetero)aroyl chlorides **5** and propargyl trityl



Scheme 3

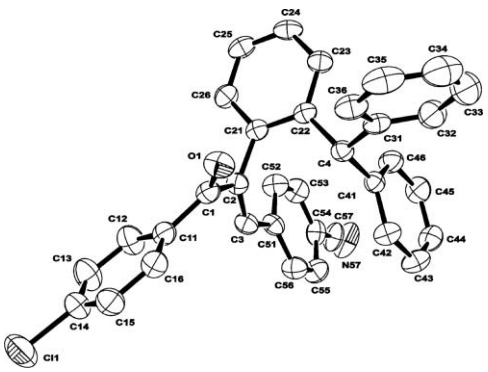
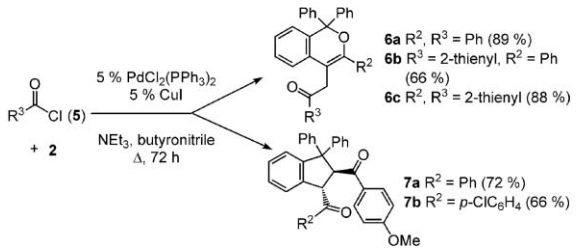


Fig. 2 Molecular structure of enone **4b** (protons and one molecule of acetone were omitted for clarity, ORTEP: 50% probability).



Scheme 4 Coupling–isomerization–Claisen rearrangement–6π electrocyclization domino sequence to 1*H*-isochromenes **6** and indans **7**.

ethers **2** were submitted to the reaction conditions of the CI–Claisen sequence. Most interestingly, neither tricyclo[3.2.1.$0^{2,7}$]oct-3-enes **3** nor enones **4** are formed, but 1*H*-isochromenes **6** and indans **7** are isolated in good to excellent yields (Scheme 4).¶ For both classes of compounds, the molecular structures were corroborated by X-ray structure analyses of 1*H*-isochromene **6b** and indan **7a** (Fig. 3 and Fig. 4).‖

In all four cases, tricyclo[3.2.1.$0^{2,7}$]oct-3-enes, enones, 1*H*-isochromenes, and indans, the product analyses readily account for congruent and related initial steps followed by mechanistic dichotomies in the conclusion of the sequences. Mechanistically, these new CI hetero domino sequences can be rationalized as follows (Scheme 5).

The CIR of electron deficient halides **8** and 1-(hetero)aryl propargyl trityl ethers **2** furnishes in all cases allenyl trityl ethers **9**

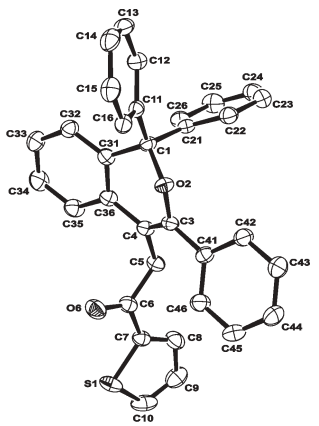


Fig. 3 Molecular structure of isochromene **6b** (protons and one molecule of chloroform were omitted, ORTEP: 50% probability).

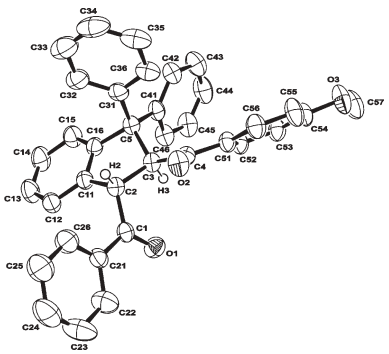
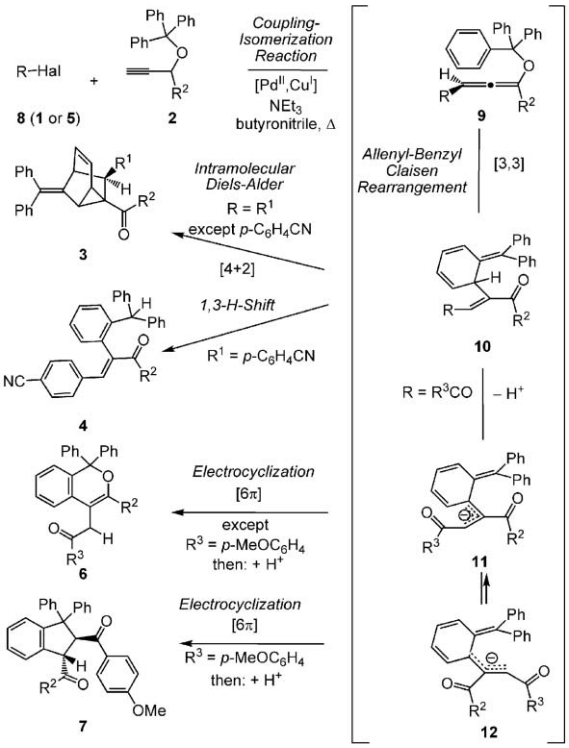


Fig. 4 Molecular structure of indan **7a** (most protons were omitted for clarity, ORTEP: 50% probability).



Scheme 5 Mechanistic rationale of the CI–Claisen domino sequences.

that undergo a [3,3]-sigmatropic rearrangement (allenyl–benzyl Claisen rearrangement) to give 5-vinyl-1,3-cyclohexadiene as common intermediates **10**. The initial products **10** undergo intramolecular cycloadditions[7] for all electron deficient (hetero)aryl substituents, except for *para*-cyanophenyl in combination with modestly electron withdrawing and releasing aryl propargyl derivatives. The sequence concludes with an intramolecular [4 + 2] cycloaddition to give tricyclo[3.2.1.$0^{2,7}$]-oct-3-enes **3**. Cyano groups tend to stabilize radicals,[8] therefore, for *para*-cyanophenyl substitution and electron withdrawing and releasing aryl propargyl substrates the resulting products are enones **4**, resulting from an aromatizing 1,3-H shift.

(Hetero)aroyl substituents are significantly stronger electron withdrawing groups. As a consequence, deprotonation of **10** should readily furnish vinylogous enolates **11**. Here, the electron withdrawing capacity of the carbonyl group influences the equilibrium **11**/**12**. Stronger electron withdrawing aryl groups on the carbonyl group favor the *Z*-isomer **11** leading to 1*H*-isochromenes **6** *via* a 6π electrocyclization of the heterotriene moiety and protonation. On the other hand the electron rich anisyl group favors the formation of the *E*-isomer **12**. Now, 6π electrocyclization of the pentadienide and protonation furnish indans **7** with *trans*-configured acyl groups.

In conclusion, we have discovered new domino reactions based upon CI–Claisen–pericyclic sequences that are highly sensitive to the electronic nature of the substitution pattern of the reactants. Studies addressing the synthetic scope of these new domino reactions and the elucidation of the electronic effects causing the observed dichotomies are currently underway.

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Notes and references

§ All new compounds have been fully characterized spectroscopically and by correct elemental analysis and HRMS.

¶ **General procedure:** To a deaerated mixture of 6 mL of butyronitrile and 6 mL of triethylamine in an oven dried screw capped vessel were added successively 1.50 mmol of the electron deficient halide **8** (**1** or **5**), 1.65 mmol of the 1-aryl propargyl trityl ethers **2**, 53 mg (0.08 mmol) of $PdCl_2(PPh_3)_2$, and 14 mg (0.07 mmol) of CuI. The solution was stirred at room temperature for 1 h, and then heated to reflux temperature for 16–72 h. After work-up, chromatography on silica gel (hexane–ethyl acetate, 2 : 1) and crystallization the products **3**, **4**, **6**, or **7** were obtained as colorless crystals.

‖ **Crystallographic data: 3a**. $C_{34}H_{29}NO_2S$, M = 515.6, triclinic, space group $P\bar{1}$, a = 10.7645(4), b = 10.8448(3), c = 13.3319(5) Å, α = 78.687(1), β = 69.861(1), γ = 68.875(1)°, V = 1358.37(8) Å^3, T = 200(2) K, Z = 2, ρ = 1.26 g cm^{-3}, crystal dimensions 0.25 × 0.13 × 0.10 mm^3, Mo K$_\alpha$ radiation, μ = 0.15 mm^{-1}, λ = 0.71073 Å. Data were collected on a Bruker Smart APEX diffractometer and a total of 5133 of the 12447 reflections were unique [R_{int} = 0.0416]. Refinement on F^2, w$R2$ = 0.096 (observed reflections), $R1$ = 0.045 for [$I > 2\sigma(I)$]. **4b**. $C_{35}H_{24}ClNO$, M = 510.0, triclinic, space group $P\bar{1}$, a = 9.1420(3), b = 11.3244(4), c = 14.2565(5) Å, α = 71.900(1), β = 89.355(1), γ = 77.085(1)°, V = 1364.72(8) Å^3, T = 200(2) K, Z = 2, ρ = 1.24 g cm^{-3}, crystal dimensions 0.32 × 0.22 × 0.14 mm^3, Mo K$_\alpha$ radiation, μ = 0.17 mm^{-1}, λ = 0.71073 Å. Data were collected on a Bruker Smart APEX diffractometer and a total of 6191 of the 14158 reflections were unique [R_{int} = 0.0405]. Refinement on F^2, w$R2$ = 0.107 (observed reflections), $R1$ = 0.049 for [$I > 2\sigma(I)$]. **6b**. $C_{34}H_{25}Cl_3O_2S$, M = 603.95, triclinic, space group $P\bar{1}$, a = 8.9794(3), b = 11.1754(4), c = 14.8724(6) Å, α = 87.793(1), β = 74.637(1), γ = 88.191(1)°, V = 1437.67(9) Å^3, T = 200(2) K, Z = 2, ρ = 1.39 g cm^{-3}, crystal dimensions 0.30 × 0.22 × 0.08 mm^3, Mo K$_\alpha$ radiation, μ = 0.42 mm^{-1}, λ = 0.71073 Å. Data were collected on a Bruker Smart APEX diffractometer and a total of 6549 of the 15088 reflections were unique [R_{int} = 0.0349]. Refinement on F^2, w$R2$ = 0.104 (observed reflections), $R1$ = 0.043 for [$I > 2\sigma(I)$]. **7a**. $C_{36}H_{28}O_3$, M = 508.58, monoclinic, space group $P2_1/c$, a = 8.905(4), b = 30.80(1), c = 10.012(5) Å, α = 90, β = 99.91(1), γ = 90°, V = 2705(2) Å^3, T = 200(2) K, Z = 4, ρ = 1.25 g cm^{-3}, crystal dimensions 0.24 × 0.14 × 0.10 mm^3, Mo K$_\alpha$ radiation, μ = 0.08 mm^{-1}, λ = 0.71073 Å. Data were collected on a Bruker Smart APEX diffractometer and a total of 2777 of the 14007 reflections were unique [R_{int} = 0.1048]. Refinement on F^2, w$R2$ = 0.108 (observed reflections), $R1$ = 0.047 for [$I > 2\sigma(I)$]. CCDC 610545–610548. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b609669g

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