NMR tube and wine solution (100 and 300 μL) added. The area of the integral for dichloroacetic acid was normalized to the areas from malate and tartrate and the concentrations calculated.

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New Efficient Multicomponent Reactions with C–C Coupling for Combinatorial Application in Liquid and on Solid Phase**

Armin de Meijere,* Hanno Nüske, Mazen Es-Sayed, Thomas Labahn, Maarten Schroen, and Stefan Bräse*

Dedicated to Dr. Pol Bamelis on the occasion of his 60th birthday

Elegance in chemical synthesis is reflected in the art of finding simple ways to construct complex structures.[1] In the age of combinatorial chemistry,[2] multicomponent and domino reactions[3] are of special importance. This is especially true for liquid-phase combinatorial chemistry,[4] in which the usually required and always relatively time-consuming purification often limits the practical sequences to a few steps.[5] In the continuing development of classic multicomponent reactions, for example those developed by Ugi,[6a] Biginelli,[6b] and Mannich,[6c] the preferential formation of heteroatom – carbon bonds is prominent. We were recently able to extend the repertoire of less common cascade reactions solely leading to

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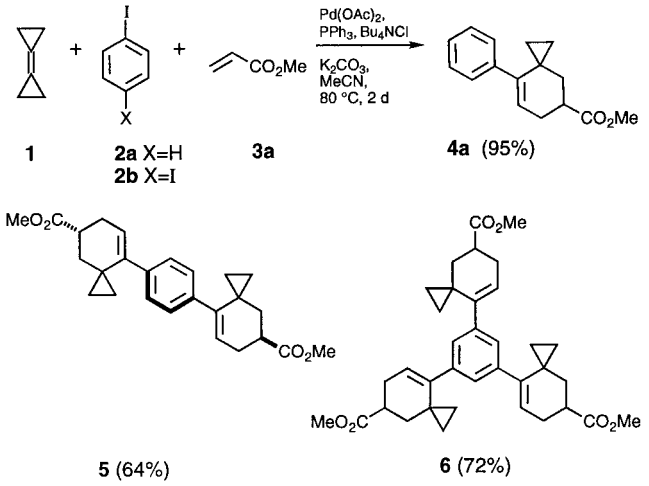
carbon–carbon bonds, for example those developed by Robinson,[6d] Baylis-Hillman,[6e] and Grieco,[6f] by a genuine three-component reaction. A highly reactive alkene, an alkenyl or aryl halide and a dienophile react with each other in a domino Heck–Diels–Alder reaction to give spiro[2.5]octene derivatives, in the course of which three C–C bonds are formed with high regioselectivity.[7]

In the meantime the yield of the reaction of bicyclopropylidene (**1**) with iodobenzene (**2a**) and methyl acrylate (**3a**) has been improved to 95% by working at higher concentration levels (Scheme 1). Under the optimized reaction conditions,[8] the even more complex symmetrical system **5** was obtained



Scheme 1. Three- and five-component reactions for the synthesis of spiro[2.5]octene derivatives.

from 1,4-diiodobenzene (**2b**) in 64% yield, and after 48 h at 80 °C and a pressure of 10 kbar the product **5** of double coupling and double [4+2] cycloaddition was isolated in 87% yield. Therefore even this formal five-component reaction proceeds completely unambiguously with the formation of six C–C bonds.[9] The reaction product is obtained as a single diastereomer and was characterized as the *meso* form by crystal structure analysis; the D,L-enantiomer pair could not be detected by ^{1}H NMR spectroscopy (500 MHz) or HPLC-MS, even in the crude product (Figure 1).[10] A further improvement was achieved by using 1,3,5-triiodobenzene, whose reaction with **1** and methyl acrylate furnished the triple coupling triple cycloadduct **6** in 72% yield.

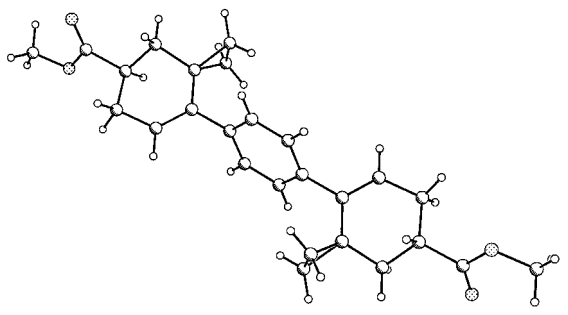
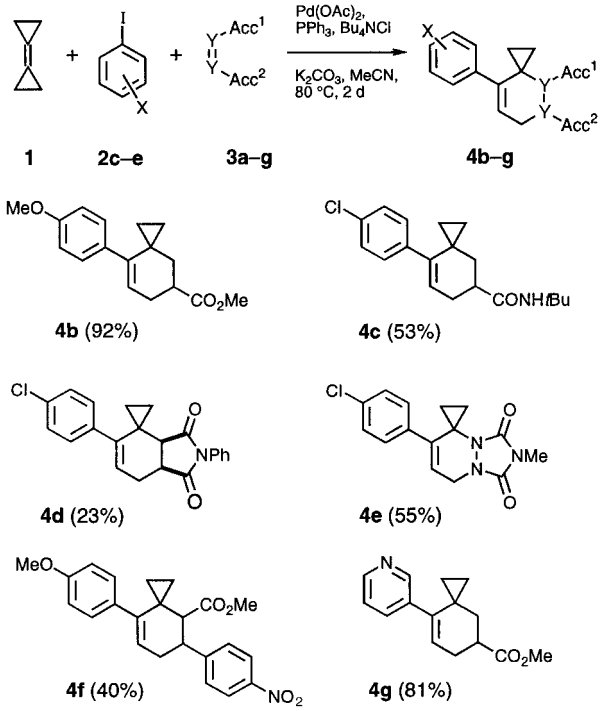


Figure 1. Structure of the double coupling double cycloadduct **5** from 1,4-diiodobenzene, bicyclopropylidene (**1**), and methyl acrylate (**3a**).

The potential of this multicomponent reaction in liquid phase combinatorial chemistry is demonstrated by the broad variability of both the iodoarene and the dienophile component (Scheme 2).[11] In the process, N-substituted maleinimides and triazoline diones do not constitute a fundamental



Scheme 2. Liquid-phase three-component combinatorial chemistry (examples).

problem, whereas 3-substituted acrylates are only of limited suitability. Thus, hardly any cycloadducts were obtained with crotonic acid, cinnamic acid, or methyl *p*-chlorocinnamate, other than with methyl *p*-nitrocinnamate. The constitution of the coupling cycloadduct **4f** isolated in 40% yield, which was formed with inverted regioselectivity compared with acrylates, was verified by X-ray structure analysis.[10]

When carried out on the solid phase, this unusual three-component reaction can be extended by a further dimension. The iodoarenyltriazenyl-substituted Merrifield resin **7**,[12] already used successfully for Heck reactions, was allowed to react with bicyclopropylidene (**1**) and methyl acrylate (**3a**) to yield the coupling cycloadduct **8** under standard conditions. In solid-phase reactions, the dimerization of the iodoarene component, a possible side reaction, is suppressed per se, and side products from the dimerization of bicyclopropylidene are easy to remove.

Reaction of the resin-bound triazenylphenyl-substituted spiro[2.5]octene **8** with trifluoroacetic acid generates the corresponding aryl diazonium salt under cleavage from the resin. This salt immediately reacts with cyclopentene or 2-ethenylpyridine in a Heck reaction in the presence of palladium acetate. After filtration from the resin, the products of the four-component reaction **9a** (as a mixture of two diastereomers in a 1:1 ratio) and **9c** were obtained in 78 and 55% yield, respectively, and with a purity >95%. The

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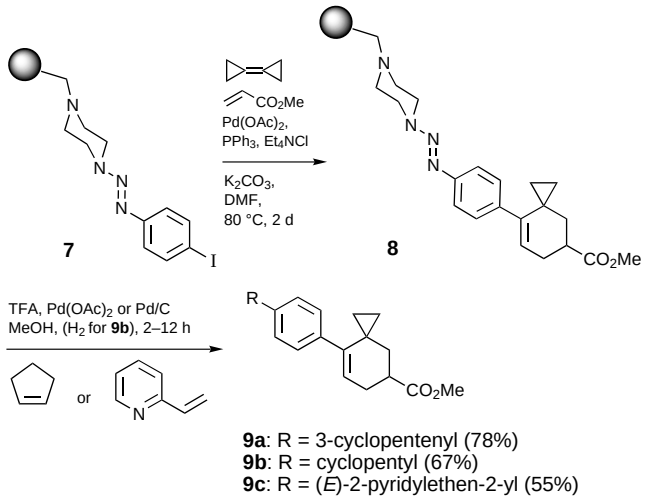
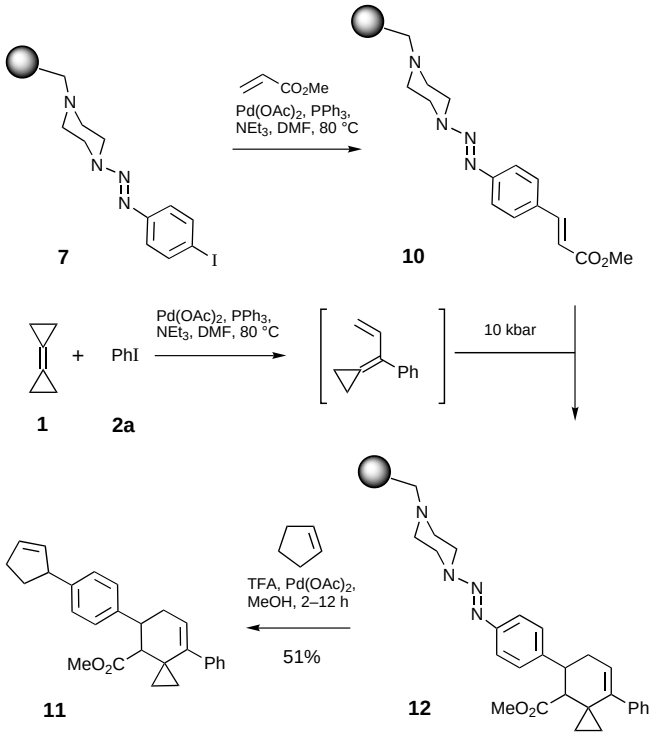
palladium-catalyzed hydrogenation of **9a** furnished the cyclopentyl derivative **9b** in 67% yield. Potential variations of this novel sequence of Heck, Diels–Alder, and a renewed Heck reaction[13] (Scheme 3) should be readily available by using a variety of alkenes in the last step.



Scheme 3. Solid-phase cleavage–cross-coupling reactions on the aryltriazenyl-substituted resin **7**. TFA = Trifluoroacetic acid.



Scheme 4. Heck–Heck–Diels–Alder–Heck reaction.

A further permutation is offered by the possibility of first coupling resin-bound triazenylphenyl iodide **7** with an acceptor-substituted alkene in a Heck reaction and then introducing the product in the domino Heck–Diels–Alder reaction with bicyclopropylidene (**1**) and iodoarenes. In fact, in analogy to the *p*-nitrocinnamate, the resin-bound, electron-deficient cinnamic acid derivative **10** obtained from **7** and methyl acrylate (**3a**) reacts under palladium catalysis with **1** and iodobenzene to give the coupling cycloadduct **12**, at least under high pressure.[14] In a subsequent Heck reaction of the diazonium ion obtained from **12** under cleavage from the resin, the novel spiro[2.5]octene **11** is obtained in 51% yield together with the side product (35%) methyl *p*-(3-cyclopentyl)cinnamate formed by Heck coupling of the diazonium ion directly formed from **10**. The success of this reaction sequence proves that the triazenyl group in **10** activates the cinnamic ester in a similarly strong way as a nitro group. This novel five-component reaction carried out in two steps, a Heck–Heck–Diels–Alder–Heck reaction sequence, also combines the simplest building blocks to form a complex molecule (Scheme 4).

With the help of these new C–C linking multicomponent reactions, relatively simple molecules can be coupled very efficiently and variably to give considerably more complex spirocyclopropane-annelated carbon skeletons. Thus, up to nine new C–C bonds are formed in a single operation.[15] The combinatorial potential of these sequences does not, however, lie solely in the variability of the starting material, but also in the diversity of combinations of different Heck variants with the Diels–Alder reaction: From the three-component reaction in the Heck–Diels–Alder sequence to the four-component reaction in the Heck–Diels–Alder–Heck sequence to the five-component reaction in the Heck–Heck–Diels–Alder–Heck sequence, the method provides true combinatorial chemistry.

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[8] Preparation of **5**: In a thick-walled 5-mL screw-cap flask, $Pd(OAc)_2$ (11.2 mg, 50 μmol, 5 mol%), PPh_3 (26.2 mg, 100 μmol, 10 mol%), bicyclopropylidene (**1**) (160 mg, 2.00 mmol), K_2CO_3 (277 mg, 2.00 mmol), Et_4NCl (166 mg, 1.0 mmol), and 1,4-diiodobenzene (166 mg, 0.500 mmol) were stirred with methyl acrylate (**3a**) (288 mg, 3.35 mmol) in anhydrous DMF (1 mL) for 48 h at 80 °C under argon. After the addition of Et_2O (15 mL), washing with H_2O (3 × 10 mL), drying over $MgSO_4$, and removal of the solvent, the residue was purified by column chromatography (column 2 × 20 cm, pentane/Et_2O (2/1)), and **5** (130 mg, 64%) was obtained as colorless crystals, $R_f = 0.32$ (Et_2O). IR (film): $\tilde{\nu} = 3078, 3047, 2927, 1734$ (C=O), 1653 cm^{-1} (C=C); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.68–0.72$ (m, 2H, cyclopropyl-H), 0.75 (m_c, 2H, cyclopropyl-H), 0.81 (m_c, 2H, cyclopropyl-H), 0.90 (m_c, 2H, cyclopropyl-H), 1.77 (dd, $^2J = 13.0$, $^3J = 3.5$ Hz, 2H, 4′-H), 2.47 (dd, $^2J = 13.0$, $^3J = 11.0$ Hz, 2H, 4′-H), 2.76 (dd, $^3J = 9.0$, $^3J = 4.0$ Hz, 4H, 6′-H), 3.18 (ddd, $^3J = 11.0$, $^3J = 9.0$, $^3J = 3.5$ Hz, 2H, 5′-H), 3.98 (s, 6H, OCH_3), 5.80 (t, $^3J = 4.0$ Hz, 2H, 7′-H), 7.08 (s, 4H, Ar-H); ^{13}C NMR (125.7 MHz, $CDCl_3$, APT): $\delta = 11.59$ (–, cyclopropyl-C), 12.91 (–, cyclopropyl-C), 20.09 (–, C-3′), 28.49 (–, C-4′), 37.48 (–, C-6′), 39.38 (+, C-5′), 51.64 (+, OCH_3), 123.80 (+, C-7′), 128.25 (+, Ar-C), 138.49 (–, C-8′*), 142.74 (–, Ar-C*), 175.98 (–, CO); MS (70 eV): *m/z* (%): 406 (31) [M^+], 183 (100) [$M^+ - 2CO - 2MeOH - C_8H_8$], 152 (6), 108 (14), 84 (14), 77 (6); elemental analysis (%): calcd. for $C_{26}H_{30}O_4$ (406.5): C 76.82, H 7.44; found: C 76.65, H 7.43.

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[10] Crystal structure analysis of **5** ($C_{26}H_{30}O_4$): $Z = 4$, $M_r = 406.52$, crystal dimensions: 0.6 × 0.5 × 0.3 mm, monoclinic, space group *P*-2(1), $a = 629.17(2)$, $b = 1069.44(3)$, $c = 1580.34(4)$ pm, $\beta = 91.311(2)°$, $V = 1.06307(5)$ nm^3, $\rho_{calcd} = 1.270$ $Mg\,m^{-3}$, $F(000) = 436$, $\lambda = 71.073$ pm, $T = 133(2)$ K, $\mu(Mo_{K\alpha}) = 0.084$ mm^{-1}. $2.30 \le 2\theta \le 25.03°$; of the 18493 collected reflections, 1882 are independent and were used for the structure refinement of 186 parameters with the help of 105 restraints. The *R* values are $R1 = 0.0804$ ($I > 2\sigma(I)$) and $wR2 = 0.1281$ (all data); min./max. residual electron density $-236/218$ $e\,nm^{-3}$. The data were collected on a Stoe-Siemens-Huber four-circle diffractometer with a Siemens-CCD surface detector. The intensities were recorded with ϕ and ω scans. The integration of the data was carried out with the programme SAINT. The structure was solved with direct methods (G. M. Sheldrick, SHELXL-93/97, program for crystal structure refinement, Göttingen University, **1997**) and refined against F^2 using the least-squares method. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were placed in geometrically ideal positions and included in the refinement. All disorders were resolved and refined anisotropically with the help of space and ADP restraints. Crystallographic data (excluding structure factors) of the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-133154 (**4f**) and CCDC-133155 (**5**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Incorporation of Magnetic Nanoparticles in New Hybrid Networks Based on Heteropolyanions and Polyacrylamide**

Cédric R. Mayer, Valérie Cabuil,* Thierry Lalot, and René Thouvenot

Hybrid organic–inorganic materials have received increasing attention over the last few years[1] as a result of the specific properties. This is due to a synergy between both organic and inorganic parts. Functionalized polyanions are good candidates for the elaboration of such materials.[2]

Herein we present a magnetic hybrid hydrogel that results from the incorporation of a magnetic particle from an aqueous dispersion into a polymeric network cross-linked by an organometallic species. The cross-linker is a new water-soluble molecular precursor in the form of a tetrafunctionalized polyoxometalate (POM) of formula $[\gamma\text{-}SiW_{10}O_{36}(RSiO)_4]^{4-}$ ($R = C_3H_6OC(O)C(Me)=CH_2$).[3] This hybrid consists of a divacant polyanion $[\gamma\text{-}SiW_{10}O_{36}]^{8-}$ unit, in

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