water (15 mL) and ice (40 g) was added, and the reaction mixture was stirred for a further 2 h during which time a black, oily solid separated out. The solution was removed by decantation, and the oily solid was dried in a vacuum desiccator. The dry residue was redissolved in dichloromethane (1 mL), placed on a silica gel column (2.5 cm × 1.5 cm), and eluted with dichloromethane. The fast-moving purple band was collected, ethanol was added, and the dichloromethane was removed under reduced pressure to yield green crystals. Recrystallization from dichloromethane/ethanol yielded pure **2** as purple crystals (12 mg, 5 %). ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C, TMS): $\delta = 1.84$ (s, 3H; SCH_3), 7.00 (d, $^3J(H,H) = 9.9$ Hz, 1H; H3), 7.95 (dd, $^3J(H,H) = 9.8$, $^3J(H,H) = 3.4$ Hz, 1H; H4), 14.00 (m, 1H; H6), 7.20 – 7.56 (m, 30H; PPh_3); $^{13}C\{^1H)$ NMR (100.6 MHz, $CDCl_3$, 24 °C, TMS): $\delta = 24.70$ (s; SCH_3), 124.10 (s; C3), 138.90 (s; C4), 144.24 (s; C5), 212.54 (t, $^2J(C,P) = 10.6$ Hz; CO), 222.69 (t, $^2J(C,P) = 6.0$ Hz; C6), 127.32 (t′, $^{2,4}J(C,P) = 9.1$ Hz; *ortho*-PPh_3), 130.00 (s; *para*-PPh_3), 132.01 (t′, $^{1,3}J(C,P) = 54.3$ Hz; *ipso*-PPh_3), 134.41 (t′, $^{3,5}J(C,P) = 10.0$ Hz; *meta*-PPh_3); IR (Nujol): $\tilde{\nu} = 1955$ (vs CO), 1526 (NO_2), 1299, 1276, 1237, 874, 843 (NO_2), 745 cm^{-1}; positive-ion FAB-MS: m/z: 1024.0479; $C_{43}H_{36}INO_3OsP_2S$ requires 1024.0473; elemental analysis calcd for $C_{43}H_{36}INO_3OsP_2S$: C 50.34, H 3.53, N 1.36, S 3.13; found: C 50.63, H 3.58, N 1.78, S 3.03.

3: Complex **1** (200 mg, 0.238 mmol) was dissolved in carbon tetrachloride (50 mL), and iron powder (1.0 mg, 0.018 mmol) was added. A solution of Br_2 (12.2 mg, 0.238 mmol) in carbon tetrachloride (10 mL) was added dropwise to the blue solution. The reaction flask was heated on a water bath at 40 °C for 1 h. The carbon tetrachloride was removed in vacuo, and the green solid was dissolved in dichloromethane (1 mL) and placed on a silica gel column (2.5 cm × 1.5 cm). The blue-green fractions were collected, and $AgClO_4$ (49.4 mg, 0.238 mmol) was added. The solution was stirred for 10 min, during which time a flocculant yellow solid appeared. The solution was then filtered through Celite, and NaI (71 mg, 0.48 mmol) in ethanol/water (10 mL/1 mL) was added. Removal of the dichloromethane, addition of ethanol (20 mL), and subsequent recrystallization of the crude product from dichloromethane/ethanol yielded dark green crystals of pure **3** (105 mg, 45 %). ^{1}H NMR (400 MHz, $CDCl_3$, 24 °C, TMS): $\delta = 1.65$ (s, 3H; SCH_3), 6.79 (d, $^3J(H,H) = 9.5$ Hz, 1H; H3), 7.15 (dd, $^3J(H,H) = 9.4$, $^3J(H,H) = 3.0$ Hz, 1H; H4), 12.61 (d, $^3J(H,H) = 2.9$ Hz, 1H; H6), 7.20 – 7.52 (m, 30H; PPh_3); $^{13}C\{^1H)$ NMR (100.6 MHz, $CDCl_3$, 24 °C, TMS): $\delta = 20.28$ (s; SCH_3), 110.56 (s; C5), 126.14 (s; C3), 147.75 (s; C4), 190.73 (t, $^2J(C,P) = 11.1$ Hz; CO), 210.81 (t, $^2J(C,P) = 5.5$ Hz; C6), 240.31 (t, $^2J(C,P) = 9.1$ Hz; C2), 127.36 (t′, $^{2,4}J(C,P) = 10.1$ Hz; *ortho*-PPh_3), 129.67 (s; *para*-PPh_3), 132.27 (t′, $^{1,3}J(C,P) = 55.3$ Hz; *ipso*-PPh_3), 134.39 (t′, $^{3,5}J(C,P) = 10.1$ Hz; *meta*-PPh_3); IR (Nujol): $\tilde{\nu} = 1943$ (vs CO), 1401, 1367, 1238, 1187, 922, 800, 668 cm^{-1}; positive-ion FAB-MS: m/z: 931.0697; $C_{43}H_{36}BrOOsP_2S$ requires 931.0730 $[M^+ - I]$; elemental analysis calcd for $C_{43}H_{36}BrIOOsP_2S \cdot 0.5\,CH_2Cl_2$: C 47.40, H 3.38; found: C 47.46, H 3.03.

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[10] Data for the X-ray structure analyses: **2**: crystals from benzene/ethanol, $C_{43}H_{36}INO_3OsP_2S \cdot 1.5\,C_6H_6$ ($M_r = 1142.99$); crystal dimensions $0.24 \times 0.24 \times 0.04$ mm^3; triclinic; space group $P\bar{1}$; $a = 12.2283(1)$, $b = 13.7785(2)$, $c = 14.1391(1)$ Å, $\alpha = 80.144(1)$, $\beta = 77.314(1)$, $\gamma = 78.930(1)^\circ$, $Z = 2$, $V = 2260.06(4)$ Å^3, $\rho_{calcd} = 1.680$ g cm^{-3}, $T = 203$ K; $2\theta_{max} = 56^\circ$; 22 095 total reflections of which 10 023 were unique ($R_{int} = 0.0268$); Siemens SMART CCD diffractometer, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å); empirical absorption correction ($\mu = 3.66$ mm^{-1}, $T_{min}/T_{max} = 0.473/0.867$). The structure was solved by Patterson and Fourier techniques and refined by full-matrix least squares on F^2. The asymmetric unit contains one molecule of **2** and 1.5 molecules of benzene. $R_1 = 0.0477$ for the 8702 observed data ($I > 2\sigma(I)$) and $wR_2 = 0.1334$ for all data; GOF(F^2) = 1.027. **3**: crystals from dichloromethane/ethanol, $C_{43}H_{36}BrIOOsP_2S$ ($M_r = 1059.73$); crystal dimensions $0.21 \times 0.12 \times 0.08$ mm^3; orthorhombic; space group *Pbca*; $a = 14.211(2)$, $b = 22.270(5)$, $c = 24.315(3)$ Å, $Z = 8$, $V = 7695(2)$ Å^3, $\rho_{calcd} = 1.829$ g cm^{-3}, $T = 203$ K; $2\theta_{max} = 47^\circ$; 31 267 total reflections of which 5529 were unique ($R_{int} = 0.0795$); Siemens SMART CCD diffractometer, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å); empirical absorption correction ($\mu = 5.33$ mm^{-1}, $T_{min}/T_{max} = 0.401/0.675$). The structure was solved by Patterson and Fourier techniques and refined by full-matrix least squares on F^2. The asymmetric unit contains a single molecule of **3**, in which one phenyl unit of one triphenylphosphane is disordered. $R_1 = 0.0437$ for the 4190 observed data ($I > 2\sigma(I)$) and $wR_2 = 0.1086$ for all data; GOF(F^2) = 1.061. Programs used: SHELXS-97 (structure solution) and SHELXL-97 (structure refinement). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC-133773 (**2**) and CCDC-133774 (**3**). 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).

[11] The denotation t′ indicates that the signal has apparent multiplicity; $^{n,m}J(C,P)$ is the sum of the two coupling constants $^mJ(C,P)$ and $^nJ(C,P)$ as explained in: S. M. Maddock, C. E. F. Rickard, W. R. Roper, L. J. Wright, *Organometallics* **1996**, *15*, 1793 – 1803.

Highly Regio- and Stereoselective Cycloreductions of 1,6- and 1,7-Enynes Activated with a Carbonyl Functionality[**]

Chang Ho Oh,[*] Hyung Hoon Jung, Joo Sung Kim, and Seung Woo Cho

The cyclization of enynes or halodienes has been widely utilized in the synthesis of structurally complex natural and synthetic products.[1] Various 1,6- and 1,7-enynes, aided by suitable palladium catalysts, cycloisomerize to the corresponding dienes,[2] which could further serve as valuable

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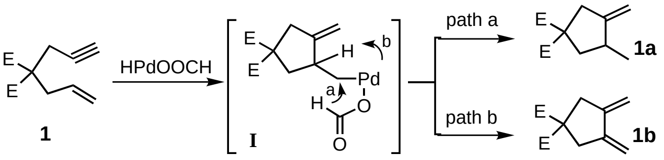
Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte or from the author.

synthetic intermediates.[3] Similar palladium catalysts, combined with silanes as hydrogen-atom donors, have been employed to reduce the alkylpalladium intermediates formed from enynes to give the corresponding mono-olefins.[4] These mono-olefins are the same products as those formed from a Bu_3SnH-mediated radical cyclization followed by destannylation.[5] Another approach leading to these products is through the cycloisomerization of 1,6-dienes.[6] We have reported that the alkylpalladium formates, where the alkyl group is derived from a coordinated enediyne, undergo direct reduction by the formate ligand prior to β-elimination of the alkyl species to give the cycloreduced products.[7] Recently, we have found that the alkylpalladium intermediate **I**, formed during catalyzed enyne cyclizations, is reductively cleaved by the formate ligand (Scheme 1).[8]

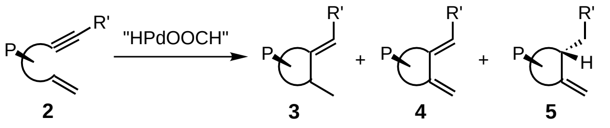


Scheme 1. Enyne **1** coordinates to the palladium-based catalyst, and intramolecular attack by the formyl group (path a) leads to cycloreduction and product **1a**; alternatively β-hydride elimination (path b) leads to product **1b**.

In order to explore the synthetic potential of this process, our efforts were directed at palladium-catalyzed cycloreductions, assisted with formic acid, for a wide variety of carbonyl-conjugated enynes.[9] In this context, Lu and Wang have reported coupling reactions of alkynes with α,β-unsaturated carbonyl compounds to form γ,δ-unsaturated carbonyl compounds.[10] Herein we report our success in forming γ,δ-unsaturated carbonyl compounds by palladium-catalyzed reactions of 1,6- and 1,7-enynes in which the alkyne moieties are conjugated with a carbonyl group.

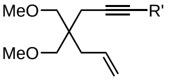
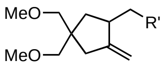
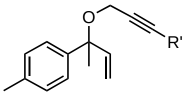
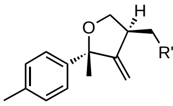
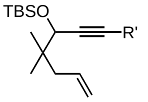
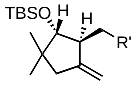
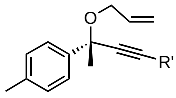
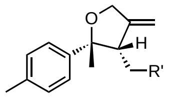
Enyne **2a** (see Table 1) was chosen as a model substrate. Palladium catalysts "HPdOOCH" were prepared in situ by mixing commercially available palladium compounds (2–5 mol%) with 1.5–3.0 equivalents of formic acid based on the amount of **2a**. Palladium compounds investigated were $Pd(OAc)_2$, $[Pd(PPh_3)_4]$, $[Pd_2(dba)_3]$, $[PdCl_2(PPh_3)_2]$, $[PdCl_2(dppe)]$, and $[Pd_2Cl_2(\pi\text{-}C_3H_5)_2]$ under various conditions. Among these palladium compounds, $Pd(OAc)_2$ and $[Pd(PPh_3)_4]$ were shown to be the most effective. Common solvents such as toluene, acetonitrile, and DMF were also tested. We established the optimal conditions as: toluene as solvent, palladium acetate as catalyst (5 mol%), triphenylphosphane as ligand (10 mol%), and formic acid as a reductant (1.5 equiv). The palladium-catalyzed cycloreduction of the enyne **2a** was expected to give the corresponding α,β-unsaturated compound **3a** according to the proposed mechanism (path a) shown in Scheme 1. Under the optimized conditions, enyne **2a** seemed to be initially cyclized to the dienoate **4a**, which was eventually converted to the γ,δ-unsaturated compound **5a** without forming any detectable amount of the expected product **3a**. This initial result prompted us to further examine the possibility of a straightforward approach to γ,δ-unsaturated carbonyl compounds.

We prepared the easily accessible enynes **2b**–**j** and followed their cyclizations under the above-mentioned conditions [Eq. (1)], and the results are summarized in Table 1.



(1)

Table 1. Palladium-catalyzed cycloreductions of enynes according to Equation (1).[a]

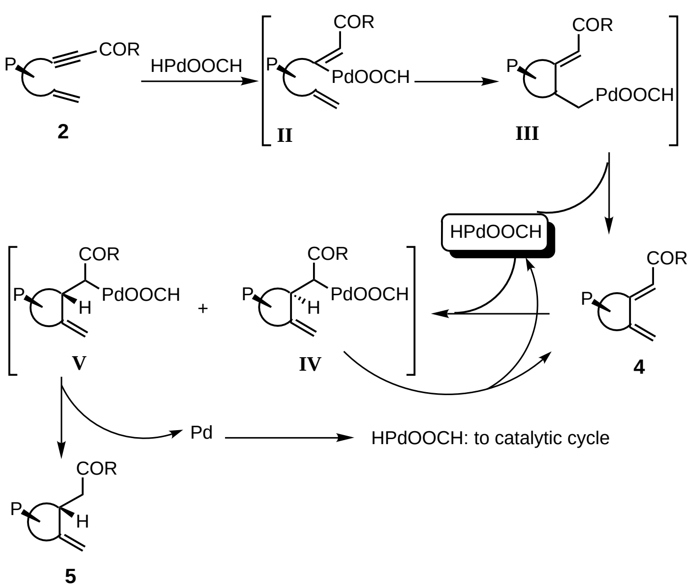
Substrates		R′	T[°C], t[h]	Products		Yield
	**2a**	$COCH(CH_3)_2$	60, 3		**5a**	81
	2b	COOEt	60, 3		**5b**	62[b]
	**2c**	COOEt	65, 2		**5c**	65[c]
	2d	CoPh	65, 2		**5d**	90
	2e	$COCH(CH_3)_2$	65, 2		**5e**	68
	2f	$CONEt_2$	60, 5		**5f**	70
	2g	$CONPh_2$	65, 2		**5g**	60
	**2h**	COPh	60, 2		**5h**	72
	2i	$CONPh_2$	80, 0.5		**5i**	65
	**2j**	COOEt	60, 12		**5j**	40[d]

[a] Catalyst: 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, 1.5–3.0 equiv HCOOH; substrate **2**: 0.3 M in toluene. [b] Isolated as a 1:5 mixture of the products **3b** and **5b**. [c] About 20% of its epimer was present. [d] Its epimer epi-**5j** (9%) was also isolated.

Several features are noteworthy. First, we demonstrated that this method allows regioselective cycloreductions of carbonyl-conjugated enynes **2a**–**j** to the corresponding γ,δ-unsaturated carbonyl compounds **5a**–**j** in high yields. Second, aliphatic and aromatic ketone, ester, and amide groups assisted the initial hydropalladation under mild conditions: all reactions were completed within 2–10 h at 60–80 °C. Even the highly sterically hindered enyne **2j** underwent cycloreduction to the corresponding products **5j** and its epimer epi-**5j** in 40% and 9% yields, respectively. Finally, we should emphasize the excellent stereoselectivity, showing that the enynes **2d**–**i** were cycloreduced to the γ,δ-unsaturated carbonyl compounds **5d**–**i** along with their epimers in diastereomer ratios ranging from 4:1 to greater than 99:1, as determined by ^1H NMR analyses of the crude products.

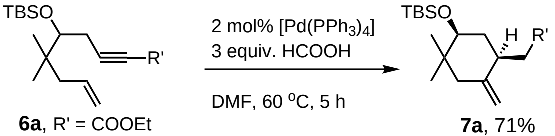
When a catalytic amount of formic acid (10 mol%) was employed for the enyne **2g**, we isolated the corresponding diene **4g** in 72% yield.[11] In a separate experiment, addition of a stoichiometric amount of formic acid to the diene **4g** in the presence of the palladium catalyst was shown to furnish the γ,δ-unsaturated product **5g** in 64% yield. These observations suggested that the reaction involves two steps: palladium-catalyzed cycloisomerization to the corresponding diene **4**, followed by reduction into the γ,δ-unsaturated products **5** mediated by hydropalladium formate. It is worth noting here that hydrogenation of 1,3-dienes conjugated with a carbonyl group, such as **4**, have been studied by Cortese and Heck.[12] They found that, with 1.1 equiv of formic acid and a palladium catalyst, the conjugated dienone β-ionone was mainly reduced to the corresponding γ,δ-unsaturated enone, while methyl sorbate was mainly reduced to methyl 2-hexenoate along with the side-product methyl 5-hexenoate.

The relative configurations of representative products (**5c**, **5i**, and **5j**) were unambiguously determined by NOESY experiments. These NMR experiments were also undertaken to clarify some mechanistic details of the cycloreductions, and why, in contrast to our original expectation, they do not lead to the thermodynamically more stable products. One might speculate that hydropalladation of the diene **4** gave a diastereomeric mixture of the intermediates **IV** and **V** (Scheme 2). While the intermediate **V** formed by attack at the more-hindered face of the carbonyl-conjugated diene **4** would undergo reductive cleavage to the thermodynamically stable product **5**, the intermediate **IV** resulting from attack at the less-hindered face might undergo the reverse reaction, β-elimination, to reproduce the carbonyl-conjugated diene **4**. Repeating the above processes could result in high stereoselectivity during formation of product **5**.



Scheme 2. Carbonyl-conjugated enyne **2** offers two possiblities to coordinating to the palladium-based catalyst (**II**, **III**) to form the carbonyl-conjugated diene **4** after β-elimination. Diene **4** may then in turn coordinate to the catalyst to form two diastereoisomers (**IV**, **V**). Intermediate **IV** β-eliminates back to **4** and the catalyst, whereas the reductive cleavage of **V** produces **5** regio- and stereoselectively.

We have extended this method to the 1,7-enynes **6a** and **6b**, activated with electron-withdrawing ester and ketone groups, respectively. These enynes, under the above reaction conditions, underwent cycloreductions in moderate yields. Optimization experiments led to a dramatically improved reaction efficiency [Eq. (2)]. Enyne **6a** was converted to the γ,δ-unsaturated ester **7a** as a single diastereomer in 71% yield.[13] When a catalytic amount of formic acid was used under similar conditions, we also detected the corresponding diene, analogous to **4**, as a major product that was reduced further to the γ,δ-unsaturated ester **7a** upon addition of an equivalent of formic acid to the reaction mixture. Likewise, the 1,7-enyne **6b**, activated with a ketone group, furnished the desired γ,δ-unsaturated ketone **7b** in 87% yield. It was proven by NOESY experiments that product **7b** has the more stable *cis* configuration.



6a, R' = COOEt
6b, R' = COCH(CH$_3$)$_2$

7a, 71%
7b, 87%

(2)

In conclusion, we have shown that cycloreductions of 1,6- and 1,7-enynes, in which the alkyne unit is conjugated with an electron-withdrawing group, provide an entry to γ,δ-unsaturated compounds like **5** and **7** in a highly regio- and stereoselective manner. Mechanistically, the reaction proceeds in two consecutive steps: β-elimination to the carbonyl-conjugated dienes **4**, then regio- and stereoselective reduction to the γ,δ-unsaturated carbonyl compounds **5**. The present study should be of considerable use for syntheses of γ,δ-unsaturated carbonyl compounds and also should be of importance for mechanistic insight into enyne cyclizations.

Experimental Section

Typical procedure for cyclization of enyne **2a**: In a 5 mL test tube the enyne **2a** (38.0 mg, 0.15 mmol), PPh$_3$ (3.9 mg, 0.015 mmol), Pd(OAc)$_2$ (1.7 mg, 0.0075 mmol), and dry toluene (0.5 mL) were added. The resulting mixture was treated with HCOOH (10 µL, 0.26 mmol) under an Ar atmosphere. The mixture was stirred for 10 min at room temperature and for 3 h at 60 °C. The reaction mixture was concentrated and separated by silica gel chromatography (eluent: ethyl acetate/hexane (5/95)) to give the cyclized product **5a** (31.1 mg, 81%) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 4.85$ (d, $J = 2.0$ Hz, 1H), 4.69 (d, $J = 2.0$ Hz, 1H), 3.34 (s, 3H), 3.38 (s, 3H), 3.24 (s, 4H), 3.00 (m, 1H), 2.74 (dd, $J = 16.8$, 5.2 Hz, 1H), 2.61 (sept, $J = 6.8$ Hz, 1H), 2.48 (dd, $J = 16.8$, 8.4 Hz, 1H), 2.28 (s, 2H), 1.96 (dd, $J = 12.8$, 8.0 Hz, 1H), 1.12 (d, $J = 6.8$ Hz, 3H), 1.11 (d, $J = 6.8$ Hz, 3H), 1.11 (dd, $J = 12.8$, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 217.20$, 154.36, 105.12, 75.63, 74.76, 59.33, 59.28, 45.76, 45.53, 41.13, 39.43, 38.51, 37.42, 18.33, 18.28; FT-IR (neat): $\tilde{\nu} = 2962$, 2928, 2875, 1711, 1650, 1455, 1206, 1158, 1107 cm^{-1}; HRMS for C$_{15}$H$_{26}$O$_3$ (M^+): calcd: 254.1882; found: 254.1880.

Characterization data for the products **5a–j** and **7a**, **b** and NOESY experimental data for **5c**, **5i**, **5j**, and **7b** is found under the Supporting Information.

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[13] All products **5a–j** and **7a**, **b** were characterized by ^{1}H and ^{13}C NMR, FT-IR, and high resolution mass spectra, and were shown to be stereochemically pure (detection limits $>99{:}1$) unless otherwise noted.

Guest-Templated Selection and Amplification of a Receptor by Noncovalent Combinatorial Synthesis**

Mercedes Crego Calama, Peter Timmerman, and David N. Reinhoudt*

Template-directed synthesis, using molecular recognition to favor the formation of one particular product, plays an essential role in important biological processes, such as protein synthesis and self-replication. It has been widely used in a variety of macrocyclization reactions[1] and (in)organic self-assembly processes.[2] Molecular imprinting of synthetic receptors by guest templation, a process first realized in polymers,[3] has recently received enormous attention as a way to direct the molecular evolution of a dynamic mixture of synthetic receptors.[4–7] Thermodynamic equilibration of these receptor systems is achieved through the reversible formation of *covalent* bonds, namely, *cis–trans* isomerization,[4] trans-esterification,[5, 8] or disulfide bond formation.[6] Here we describe the first example of guest-templated selection of a receptor in a dynamic *noncovalent* combinatorial mixture, in which the different receptors equilibrate through the reversible formation of multiple hydrogen bonds.

Recently we have reported[9] the noncovalent synthesis[10] of a family of hydrogen-bonded assemblies $\mathbf{1}_3\cdot(\mathrm{DEB})_6$ (DEB = 5,5-diethylbarbituric acid), consisting of nine different components held together by 36 cooperative hydrogen bonds. Structural diversity at the supramolecular level can be generated in an extremely simple way, by mixing the various components **1** (**a**, **b**, …*N*; Figure 1) under thermodynamically controlled conditions.[11] In this way a library of 220 different noncovalent assemblies can be synthesized simply by assembling a mixture of ten different components derived from **1**.[12] The composition of these libraries is statistical as determined for the model system $\mathbf{1a}_{3-n}\cdot\mathbf{1b}_n\cdot(\mathrm{DEB})_6$ ($n = 0-3$), which exists as a 1:1:3:3 mixture of homomeric ($\mathbf{1a}_3\cdot(\mathrm{DEB})_6$ and $\mathbf{1b}_3\cdot(\mathrm{DEB})_6$) and heteromeric ($\mathbf{1a}\cdot\mathbf{1b}_2\cdot(\mathrm{DEB})_6$

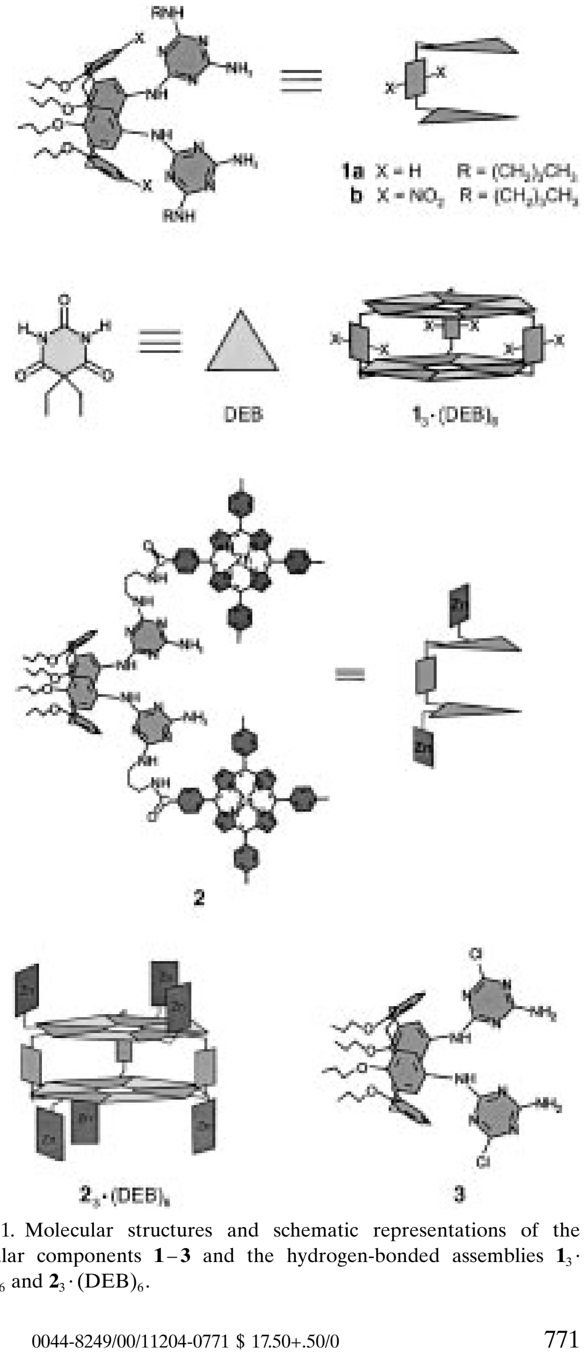

Figure 1. Molecular structures and schematic representations of the molecular components **1–3** and the hydrogen-bonded assemblies $\mathbf{1}_3\cdot(\mathrm{DEB})_6$ and $\mathbf{2}_3\cdot(\mathrm{DEB})_6$.

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