Experimental Section

Steady-state absorption and fluorescence spectroscopy: Bruins Instruments Omega 10 spectrophotometer, Spectronics Instruments 8100 spectrofluorometer; details on the determination of the relative fluorescence quantum yields (Φ_f) and the correction of the fluorescence spectra are given in ref. [7b]; fluorescence standards: cresyl violet in methanol ($\Phi_f = 0.54 \pm 0.03$),[17a] rhodamine 101 in ethanol ($\Phi_f = 1.00 \pm 0.02$).[17b]

Time-resolved fluorescence spectroscopy: Unique laser impulse fluorometer with ps time resolution as described in ref. [17c] including a synchronously pumped dye (rhodamine 6G) laser (Spectra Physics); details on detection and temporal calibration are given in ref. [7b, 17c]; fitting procedure: reference convolution of cresyl violet decays (Globals Unlimited V2.2, Laboratory for Fluorescence Dynamics, University of Illinois).

Cyclic voltammetry: Solvent dichloromethane; reversible half-wave potentials $E_{1/2}$ [mV] versus ferrocene/ferrocenium as internal standard; conditions: scan rate 250 mV s^{-1}, supporting electrolyte: 0.1 M tetrabutylammonium hexafluorophosphate (TBAHFP).

Spectroelectrochemistry: Solvent dichloromethane, OTTLE transmission cell with a minigrid-gold working electrode.[18]

Synthesis: 1,3,5,7-Tetramethyl-8-phenyl-difluorobordiazaindacene (65 mg, 0.2 mmol) [7b] and 4-dimethylaminobenzaldehyde (35 mg, 0.23 mmol) were refluxed for 26 h in a mixture of toluene (5 mL), glacial acetic acid (0.15 mL) and piperidine (0.18 mL) together with a small amount of molecular sieves (3 Å). After cooling to room temperature the mixture was placed on top of a silica column and eluted with CH_2Cl_2/hexane (1/1). The blue fraction was collected and recrystallized from $CHCl_3$/hexane to give **1** as purple needles (22 mg, 0.048 mmol, 24 %). M.p.: 288 – 291 °C; IR (KBr, $\tilde{\nu}$ in cm^{-1}): $\tilde{\nu} = 1178$ (B–F); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.38$ (s, 3H), 1.42 (s, 3H), 1.54 (s, 3H), 3.03 (s, 6H), 5.96 (s, 1H), 6.59 (s, 1H), 6.70 (m, 2H), 7.20 (d, 2H, $J = 16.3$ Hz), 7.28 – 7.33 (m, 2H), 7.45 – 7.55 (m, 6H); HR-MS (EI, 70 eV): calcd for $C_{28}H_{28}N_3BF_2$ 455.2344, found 455.2352.

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[14] Note that during our studies no *trans* – *cis* isomerization was observed.

[15] No biexponential decays, rise times, or other experimental hints[7b] for an excited state reaction were found during our studies, suggesting that the Franck – Condon excited state rapidly relaxes toward the ^{1}CT state.

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An Efficient Cobalt(I) Catalyst System for the Selective 1,4-Hydrovinylation of 1,3-Dienes**

Gerhard Hilt,* François-Xavier du Mesnil, and Steffen Lüers

The selective 1,4-hydrovinylation of 1,3-dienes with alkenes under mild reaction conditions for the formation of new C–C bonds is of high synthetic interest.[1] For instance, ethylene and 1,3-butadiene are codimerised under rhodium catalysis on an industrial scale (DuPont synthesis). The resulting 1,4-hexadiene is then transformed into synthetic rubber and other unsaturated polymers.[2]

Recently we described a catalyst system ([$CoBr_2$(dppe)]/ZnI_2/Bu_4NBH_4 dppe = ethane-1,2-diylbis(diphenylphosphane)) for the efficient Diels – Alder reaction of acyclic 1,3-dienes with acetylenes.[3] When we attempted to use this catalyst system for the Diels – Alder reaction of acyclic 1,3-dienes, with substituted alkenes as the dienophile, none of the desired Diels – Alder product could be isolated. Instead the linear 1,4-hydrovinylation product **2** was isolated from the

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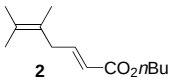
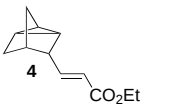
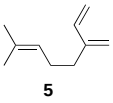
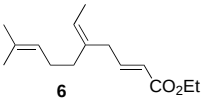
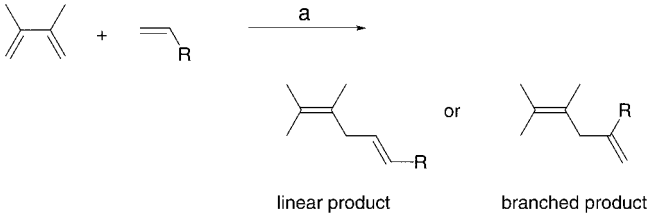
reaction of 2,3-dimethyl-1,3-butadiene (**1**) with *n*-butyl acrylate (entry 1, Table 1). This product is formed by a 1,4-addition of the acrylate to the diene under formal insertion into the (*E*)-β-C–H bond of the acrylate (Scheme 1).

Table 1. Cobalt(I)-mediated reaction of 1,3-dienes with acrylates.

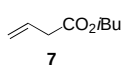
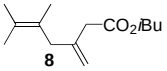
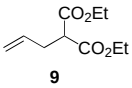
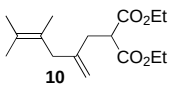
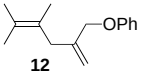
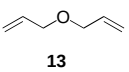
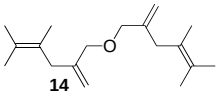
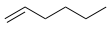
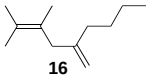
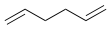
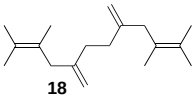
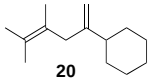
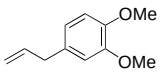
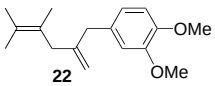
Entry	Substrate	Product	Yield [%]
1	 **1**	 **2**	92
2	 **3**	 **4**	82
3	 **5**	 **6**	88[a]

[a] In addition, 5% of the linear product ethyl 6,10-dimethyl-(*E*)-2,5,9-undecatrienoate was isolated.



Scheme 1. 1,4-Hydrovinylation of 1,3-dienes with substituted alkenes. a) [$CoBr_2$(dppe)] (1–3 mol%), ZnI_2 (3–9 mol%), Bu_4NBH_4 (1–3 mol%), CH_2Cl_2, 25 °C, 16 h.

Table 2. Cobalt(I)-mediated hydrovinylation of functionalized alkenes with 2,3-dimethyl-1,3-butadiene (**1**).

Entry	Substrate	Product	Yield [%]
1	 **7**	 **8**	97[a]
2	 **9**	 **10**	81[a]
3	 **11**	 **12**	98
4	 **13**	 **14**	95
5	 **15**	 **16**	95
6	 **17**	 **18**	97
7	 **19**	 **20**	66[a]
8	 **21**	 **22**	95

[a] The reaction was performed at 40 °C and with 5 mol% of the cobalt catalyst.

The reaction of ethyl acrylate using **3** and **5** as model systems also proceed in high yield under mild reaction conditions (room temperature, 16 h, 1–3 mol% catalyst, 100% conversion). The new C–C single bond is formed predominantly at the disubstituted double bond of the monosubstituted 1,3-dienes (92:8 by GC, 88% isolated yield of **6**, entry 3, Table 1)[4]. The regiochemistry can be further improved when the reaction temperature is lowered (94:6, 0 °C).

Because of the mild reaction conditions, the 1,4-hydrovinylation products can be isolated in good to excellent yields, while the often encountered polymerization side products are not formed.[5]

Besides acrylic esters, the longer chain β,γ- and γ,δ-unsaturated carbonic esters **7** and **9** also react well with 1,3-dienes (entries 1 and 2, Table 2). In these cases the new C–C bond is formed at the more substituted carbon of the alkene, which will be referred to as "branched 1,4-hydrovinylation" (compare Scheme 1). The branched 1,4-hydrovinylation products are also formed with allyl ethers **11** and **13** (entries 3 and 4, Table 2), and the products are isolated in excellent yields (98% and 95%, respectively) with a high level of selectivity (>98%). Even unfunctionalized terminal alkenes (**15**, **17**, and **19**; Table 2, entries 5–7) undergo this hydrovinylation to give the branched products with high selectivities and good yields. The C–C bond formation of these substrates also proceeds under mild reaction conditions so that with the nonconjugated 1,5-diene **17** no isomerization could be detected. Although, more sterically hindered alkenes such as **19** react more slowly than the unbranched terminal alkenes (e.g. **15** and **17**), the 1,4-hydrovinylation product is still formed exclusively. Allyl phenyl ethers can be used successfully as starting materials (entry 3, Table 2) and these materials can be converted by a Claisen rearrangement into allyl benzene derivatives. The direct conversion of allyl benzene derivatives (like **21**) with 1,3-dienes can also be accomplished under mild reaction conditions by using our catalyst system and the product can be isolated in a very good yield of 95% (entry 8, Table 2).

The 1,4-hydrovinylation reaction of silyl-substituted alkenes (vinyl and allyl silanes) generates the branched, silyl-substituted 1,4-dienes (Table 3),[6] which are interesting building blocks for further transformations. The branched 1,4-hydrovinylation reactions generally proceed in good yields while the new C–C bond is formed with high regioselectivity at the less-substituted double bond of the diene (**26**, 83%, 94:6). These silyl-substituted derivatives are easily converted under acid catalysis into the conjugated 1,3-dienes. For example, **25** is quantitatively isomerized to (*E*/*Z*)-trimethyl-(2,4,5-trimethyl-hexa-2,4-dienyl)silane. The chemistry of such

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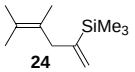
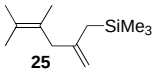
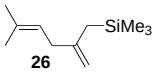
Table 3. Cobalt(I)-mediated hydrovinylation of silyl substituted alkenes with 1,3-dienes.

Entry	Substrates	Product	Yield [%]
1	 	 **24**	90
2	 	 **25**	92
3	 	 **26**	83

masked carbon nucleophiles is well described and very interesting transformations seem possible with these higher-substituted vinyl and allyl silanes.[7]

In conclusion, interesting linear and branched 1,4-dienes can be generated under very mild reaction conditions with good selectivities and in good to excellent isolated yields from the 1,4-hydrovinylation reactions. The investigation of reactions with higher-substituted functionalized alkenes and nonsymmetrical 1,3-dienes are currently underway.

Experimental Section

Representative procedure (synthesis of 4,5-dimethyl-2-methylene-4-hexenyloxybenzene (**12**)): A 50 mL flask was charged with [$CoBr_2$(dppe)](40 mg, 65 μmol, 1.8 mol%) and dry zinc iodide (100 mg, 313 μmol, 8.6 mol%) under nitrogen atmosphere and suspended in dry dichloromethane (2.0 mL). After the addition of 2,3-dimethyl-1,3-butadiene (0.5 mL, 363 mg, 4.42 mmol) and allyl phenyl ether (0.5 mL, 489 mg, 3.64 mmol), tetrabutylammonium borohydride (18 mg, 70 μmol, 1.9 mol%) was added, inducing a color change from green to brown. The mixture was stirred overnight at room temperature, then pentane (10 mL) was added and the solution filtered through silica gel with pentane/diethyl ether (10/1) as the eluent. The filtrate was reduced in volume and the product purified by column chromatography on silica gel with pentane/diethyl ether (50/1) as the eluent. The product **12** was obtained as a colorless liquid (772 mg, 3.57 mmol, 98% yield).

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Subnanomolar Inhibitors from Computer Screening: A Model Study Using Human Carbonic Anhydrase II

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The search for novel lead structures as potential drugs or herbicides is increasingly time consuming and costly. Modern methods of disease characterization at the molecular level, driven in particular by the Genome Project,[1] promise to deliver a plethora of potential therapeutic targets. How well are we prepared to transform this flood of information into lead structures? Enormous effort has been put into large-scale automation of experimental hi-tech high-throughput screening (HTS). Initial euphoria surrounding this technique as a universal lead generator has subsided as a result of the considerable costs involved, coupled with frequent inadequacies in quality and quantity of the available compounds for screening.[2] This raises the question: are computer methods sufficiently mature to complement the experimental screening process for new lead structures?

The requirements for computer screening[3] are opposite to those for HTS. The latter is technology-driven, delivering potentially structurally diverse hits by identifying an interaction with the target. No insights are obtained into why a particular hit interacts, however. In contrast, virtual computer screening is dependent upon prior information about factors necessary for binding to the target; thus, it is knowledge-driven. Computer screening should therefore provide the interactions responsible for binding. The rules governing protein–ligand interactions are, however, complex and are only in part understood.[4] We decided to investigate whether the rules incorporated in current programs are able to reliably predict novel ligands.

We chose human carbonic anhydrase II for our test study, as its structure has been solved to high resolution. We utilized existing computational tools to analyze the binding pocket in

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