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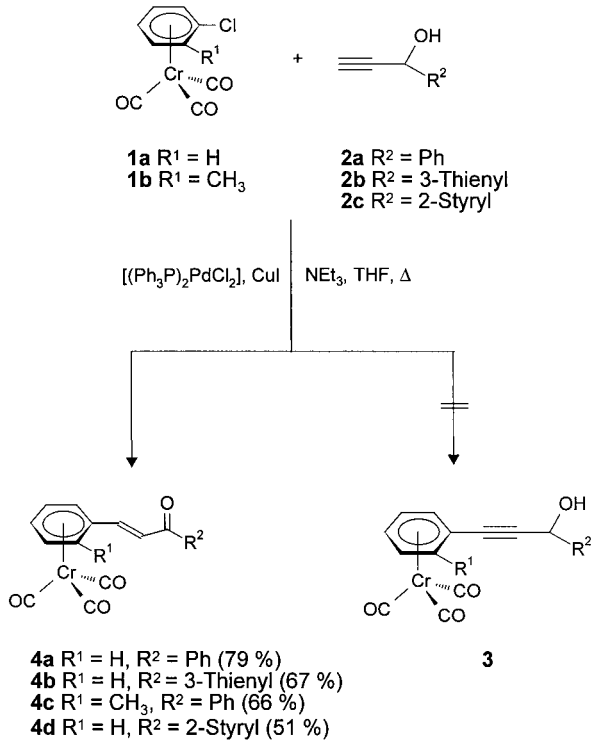
An Unexpected Coupling – Isomerization Sequence as an Entry to Novel Three-Component-Pyrazoline Syntheses**

Thomas J. J. Müller,* Markus Ansorge, and Daniel Aktah

Consecutive reactions[1] have gained increasing importance and interest since efficient syntheses inherently claim to generate a maximum of structural complexity in few steps and in good yields from simple starting materials and with high chemo-, regio-, and stereoselectivity. In such reactions, the directly preceding step forms the functionality necessary for the following transformation. Particularly with regard to multicomponent reactions, the development of novel cascade reactions for the in-situ-generation of reactive functional groups is an intensively pursued goal. Ideally, all these processes occur in a consecutive fashion, occasionally by successive addition of reagents, without the isolation of intermediates and in the sense of a "one-pot synthesis". A model for these consecutive processes are multicomponent condensations[2] as well as palladium-catalyzed cascade reactions,[3] which have proved particularly useful in many cases owing to the mild reaction conditions and the pronounced tolerance for functional groups.

In the course of our work on the chemistry of (arene)Cr-$(CO)_3$ complexes with conjugated side chains,[4] we now have found that the usually reliable Sonogashira coupling[5] of chloroarene complexes **1** with 1-aryl prop-2-ynoles **2** does not furnish the expected alkyne coupling products, the propargyl alcohols **3**, but that the isomeric aryl complexed chalcones **4**[6] are formed in good yields (Scheme 1).



Scheme 1. Synthesis of chromium carbonyl complexed chalcones by means of a coupling – isomerization sequence.

The constitution of the complexed chalcone **4a** was elucidated unambiguously by a selectively ^{1}H-decoupled ^{13}C NMR experiment, and thus, a Meyer – Schuster rearrangement could be ruled out.[7] Remarkably, the chalcones are formed with excellent *trans* selectivity ($^3J = 16$ Hz), indicating a thermodynamically controlled double bond formation.

To the best of our knowledge this unusual reaction has so far only been observed for the coupling of 2-halogen-substituted pyrimidines.[8] In this case the authors explained the mechanism by a coordination of an intermediate during a hydropalladation – dehydropalladation catalytic cycle to the heterocyclic nitrogen atom.[8c] Additionally, some transition metal catalyzed redox isomerizations of propargyl alcohols to

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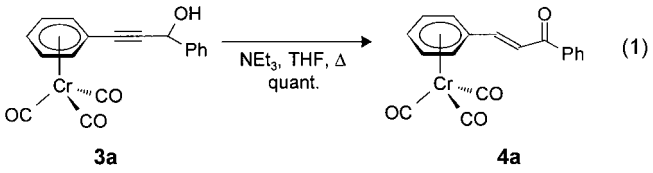
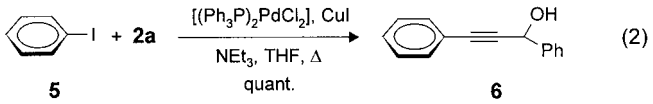
α,β-unsaturated carbonyl compounds have been described.[9] However, due to a lack of heteroatom coordination this explanation fails for the formation of the complexes **4**. Furthermore, we now could show that this isomerization exclusively occurs in a base-catalyzed manner. Thus, heating of the complexed diphenylpropargyl alcohol **3a** ($R^1 = H$, $R^2 =$ Ph), the presumed primary product of the Sonogashira coupling of **1a** with **2a**, in THF in the presence of triethylamine gives rise to a rapid formation of the complexed chalcone **4a** [Eq. (1)]. On the other hand the coupling of



3a **4a** (1)

propargyl alcohol **2a** with iodobenzene (**5**) instead of a chlorobenzene complex, which undergoes the oxidative addition at the palladium complex at a comparable rate, exclusively gives rise to the formation of the diphenylpropargyl alcohol (**6**) [Eq. (2)]. Evidently, the electronic nature



5 **6** (2)

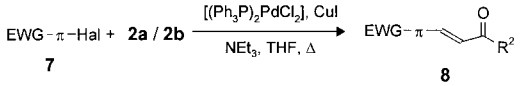
of the halogen arene component plays a key role for the following isomerization. Therefore, we assume that this coupling–isomerization sequence is far more generally applicable than only for aromatic heterocycles and chromium carbonyl complexed arenes.

For halogen components **7** (π denotes a structural unit with a π-electron system) with electron-withdrawing groups in conjugation to the halogen carbon atom as, for example, in acceptor-substituted halogen (hetero)arenes, (*Z*)-3-bromomethyl acrylate, or 3-bromocyclohex-2-enone, and for extended π-substituents at the propargylic center of **2**, the enones **8** are formed in good to excellent yields [Eq. (3); Table 1].

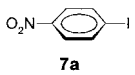
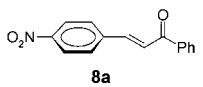
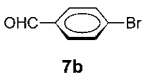
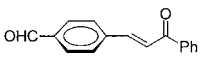
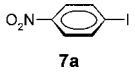
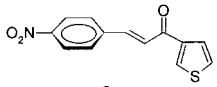
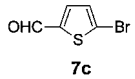
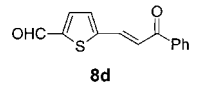
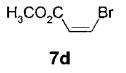
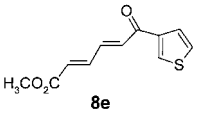
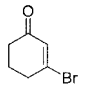
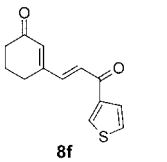
According to the product analysis and the control experiment addressing the base-catalyzed isomerization of **3a** to **4a**, the mechanistic course of this coupling–isomerization sequence can be outlined as follows (Scheme 2). The Sonogashira coupling of the terminal arylpropargyl alcohol **2** with a sufficiently electron-poor sp^2-hybridized halogen compound **7** results in the formation of an acceptor-substituted propargyl alcohol **9**. Upon deprotonation at the propargyl center with triethylamine under equilibrium conditions, a resonance-stabilized propargyl–allenyl anion **10** is formed that is protonated to give the thermodynamically more favored allene **11**. Finally, the sequence concludes with an allenol–enone tautomerism to furnish the *trans*-configured enone **8** selectively.

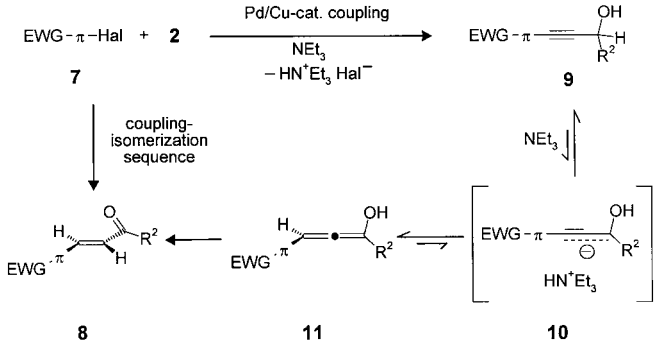
Under the mild reaction conditions the coupling–isomerization sequence turns out to be a competitive strategy for the

Table 1. Coupling–isomerization reaction.



7 **8** (3)

No.	EWG-π-Hal **7**	Propargyl alcohol **2**	Enone **8**[10]	Yield [%][11]
1	 **7a**	**2a** $R^2 =$ Ph	 **8a**	80
2	 **7b**	**2a** $R^2 =$ Ph	 **8b**	57
3	 **7a**	**2b** $R^2 =$ 3-Thienyl	 **8c**	100
4	 **7c**	**2a** $R^2 =$ Ph	 **8d**	85
5	 **7d**	**2b** $R^2 =$ 3-Thienyl	 **8e**	90
6	 **7e**	**2b** $R^2 =$ 3-Thienyl	 **8f**	97



Scheme 2. Mechanistic rationale for the course of the coupling–isomerization sequence.

synthesis of enones in comparison to aldol condensations, especially, if the required aldehyde is difficult to prepare (e.g. the corresponding 3-formylcyclohex-2-enone[12]) or if an alkaline-sensitive functionality (**7b**, **7c**, **7d**) needs to be carried through a reaction sequence without tedious protecting group manipulations. Additionally, propargyl alcohols are significantly easier to handle than vinyl ketones that can be coupled by Heck reactions to give enones but display a distinct propensity to polymerize. Interestingly, the coupling–isomerization reaction leads to a complete $Z-E$ isomerization of the acrylate double bond (**8e**[13]), which supports a thermodynamically controlled formation of the enone functionality (via delocalization of the propargyl anion intermediate). In contrast, Sonogashira couplings proceed stereospecifically with retention of alkene configuration.[5] Accordingly,

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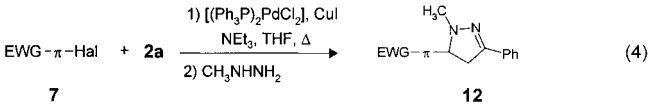
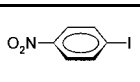
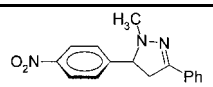
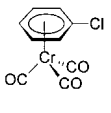
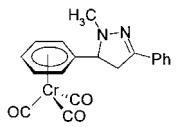
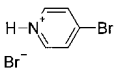
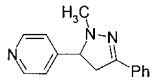
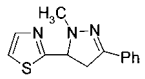
this is a facile and stereoselective access to electron-deficient dienes[14] (**8e**, **8f**), a class of interesting substrates in Diels–Alder reactions with inverse-electron demand.[15].

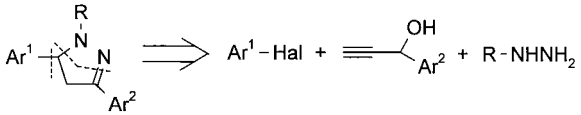
Furthermore, this mild enone synthesis enables the development of novel one-pot reactions taking advantage of the newly generated enone functionality. Thus, the addition of *N*-methylhydrazine is compatible with the reaction conditions after the coupling. Only after the base-catalyzed propargyl alcohol–enone isomerization the hydrazine enters the Michael-addition–cyclocondensation sequence with the α,β-unsaturated carbonyl compounds giving rise to the formation of 2-pyrazolines **12**[16] [Eq. (4); Table 2].

Table 2. Three-component one-pot pyrazoline synthesis.



No.	EWG-π-Hal **7**	Pyrazoline **12**[10]	Yield [%][11]
1	 **7a**	 **12a**	90
2	 **1a**	 **12b**	63
3	 **7f**	 **12c**	77
4	 **7g**	 **12d**	69

Upon applying the coupling–isomerization sequence of a haloarene, a propargyl alcohol, and a hydrazine, we have developed a novel one-pot synthesis of 3,5-disubstituted 2-pyrazolines, an important class of pharmacophores,[17] which allows unusual retrosynthetic cuts for the construction of heterocyclic systems (Scheme 3). Further heterocycle syntheses, even in a combinatorial sense, are now readily conceivable on the basis of this coupling–isomerization sequence.



Scheme 3. Retrosynthetic analysis of 3,5-diaryl-2-pyrazolines.

Experimental Section

Enone synthesis (**8a**): To a solution of **7a** (0.25 g, 1.00 mmol), $[Pd(PPh_3)_2Cl_2]$ (22 mg, 0.02 mmol), and CuI (2 mg, 0.01 mmol) in anhydrous THF (10 mL) and triethylamine (5 mL) under nitrogen, a solution of **2a** (0.14 g, 1.05 mmol) in THF (10 mL) was added dropwise over a period of 30 min. Then the reaction mixture was heated to reflux for 10 h. After the mixture had cooled to room temperature, diethyl ether (30 mL) was added and the suspension was filtered. The solvents were removed in vacuo and the crude product was flash chromatographed on silica gel (length: 10 cm, diameter: 1 cm) with diethyl ether/pentane to give **8a** (0.40 g; 80%), m.p. 161–162 °C (ref. [18] 160–161 °C). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.76$ (dd, ^3J(H,H) = 7.7 Hz, 2H; CH), 7.85 (m, 1H), 7.88 (d, ^3J(H,H) = 15.8 Hz, 1H; CH), 8.01 (d, ^3J(H,H) = 8.7 Hz, 2H; CH), 8.05 (d, ^3J(H,H) = 15.4 Hz, 1H; CH), 8.27 (d, ^3J(H,H) = 8.6 Hz, 2H; CH), 8.50 (d, ^3J(H,H) = 8.8 Hz, 2H; CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 124.14$ (CH), 125.66 (CH), 128.52 (CH), 128.76 (CH), 128.88 (CH), 133.30 (CH), 137.47 (C_{quat}), 140.98 (C_{quat}), 141.41 (CH), 148.49 (C_{quat}), 189.55 (C_{quat}).

One-pot pyrazoline synthesis (**12a**): To a solution of **7a** (0.25 g, 1.00 mmol), $[Pd(PPh_3)_2Cl_2]$ (22 mg, 0.02 mmol), and CuI (2 mg, 0.01 mmol) in anhydrous THF (10 mL) and triethylamine (5 mL) under nitrogen, a solution of **2a** (0.14 g, 1.05 mmol) in THF (10 mL) was added dropwise over a period of 30 min. Then the reaction mixture was heated to reflux for 10 h. After the mixture had been cooled, *N*-methylhydrazine (0.15 mL, 3.76 mmol) was added and heating was continued for 5 h. After removal of the solvents in vacuo the crude product was flash chromatographed on silica gel (length: 10 cm, diameter: 1 cm) with diethyl ether/pentane to furnish **12a** (0.26 g; (92%), m.p. 118–119 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 2.84$ (s, 3H, CH_3), 2.96 (dd, ^3J(H,H) = 14.0, 16.1 Hz, 1H; CH), 3.56 (dd, ^3J(H,H) = 10.1, 16.1 Hz, 1H; CH), 4.25 (dd, ^3J(H,H) = 10.1, 14.0 Hz, 1H; CH), 7.33–7.40 (m, 3H; CH), 7.61–7.68 (m, 4H, CH), 8.23 (d, ^3J(H,H) = 6.8 Hz, 2H; CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 41.78$ (CH_3), 43.54 (CH_2), 72.63 (CH), 124.02 (CH), 125.88 (CH), 128.31 (CH), 128.61 (CH), 129.05 (CH), 132.27 (C_{quat}), 147.68 (C_{quat}), 148.16 (C_{quat}), 149.81 (C_{quat}); MS (70 eV, EI), *m*/*z* (%): 281 (100)[M^+]; IR (KBr): $\tilde{\nu} = 1607$ cm^{-1}(C=N); elemental analysis (%) calcd for $C_{16}H_{15}N_3O_2$: C 68.31, H 5.37, N 14.93; found: C 68.21, H 5.47, N 14.62.

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[6] Selected physical data of **4**. **4a**: ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 5.80$ (dd, ^3J(H,H) = 6.0, 6.1 Hz, 2H; CH), 5.87 (t, ^3J(H,H) = 6.1 Hz, 1H; CH), 6.40 (d, ^3J(H,H) = 6.3 Hz, 2H; CH), 7.36 (d, ^3J(H,H) = 15.6 Hz, 1H; CH), 7.56 (dd, ^3J(H,H) = 7.3, 7.4 Hz, 2H; CH), 7.67 (t, ^3J(H,H) = 7.3 Hz, 1H; CH), 7.86 (d, ^3J(H,H) = 15.6 Hz, 1H, CH), 8.12 (d, ^3J(H,H) = 7.3 Hz, 2H; CH); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C): $\delta = 94.02$ (CH), 95.87 (CH), 95.91 (CH), 101.43 (C_{quat}), 123.24 (CH), 128.74 (CH), 129.00 (CH), 133.60 (CH), 137.32 (C_{quat}), 141.53 (CH), 188.66 (C_{quat}), 233.45 (C_{quat}); MS (70 eV, EI): *m*/*z* (%): 344 (13) [M^+], 288 (6) [$M^+ - 2$CO], 260 (100) [$M^+ - 3$CO]; IR (KBr): $\tilde{\nu} = 1966$ cm^{-1} (CO), 1891 (CO), 1667 (C=O), 1609 (C=C). **4b**: M.p. 141–143 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 5.79–5.86$ (m, ^3J(H,H) = 6.2 Hz, 3H; CH), 6.36 (d, ^3J(H,H) = 6.1 Hz, 2H; CH), 7.32 (d, ^3J(H,H) = 15.4 Hz, 1H, CH), 7.64–7.68 (m, 2H, CH), 7.76 (d, ^3J(H,H) = 15.5 Hz, 1H; CH), 8.78 (s, 1H, CH); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C): $\delta = 94.10$ (CH), 95.73 (CH), 95.77 (CH), 101.58 (C_{quat}), 124.32 (CH), 127.16 (CH), 128.09 (CH), 134.88 (CH), 140.52 (CH), 142.71 (C_{quat}), 182.35 (C_{quat}), 233.45 (C_{quat}); MS (70 eV, EI): *m*/*z* (%): 350 (17) [M^+], 294 (11) [$M^+ - 2$CO], 266 (100) [$M^+ - 3$CO]; IR (KBr): $\tilde{\nu} = 1969$ cm^{-1} (CO), 1883 (CO), 1656 (C=O), 1598 (C=C). **4c**: M.p. 92–93 °C; ^{1}H NMR (300 MHz,

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[D$_6$]DMSO, 25 °C): $\delta = 2.34$ (s, 3H; CH_3), 5.67 – 5.69 (m, 2H; CH), 5.96 (t, $^3J(H,H) = 6.3$ Hz, 1H; CH), 6.67 (d, $^3J(H,H) = 6.8$ Hz, 1H; CH), 7.55 (d, $^3J(H,H) = 15.0$ Hz, 1H; CH), 7.57 (dd, $^3J(H,H) = 7.3$, 7.4 Hz, 2H; CH), 7.67 (t, $^3J(H,H) = 7.3$ Hz, 1H; CH), 7.87 (d, $^3J(H,H) = 15.3$ Hz, 1H; CH), 8.13 (d, $^3J(H,H) = 7.5$ Hz, 2H; CH); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C): $\delta = 18.76$ (CH_3), 91.77 (CH), 94.53 (CH), 95.39 (CH), 96.86 (CH), 100.11 (C_{quat}), 124.05 (CH), 128.75 (CH), 129.02 (CH), 133.64 (CH), 137.31 (C_{quat}), 138.32 (CH), 188.59 (C_{quat}), 233.65 (C_{quat}); MS (70 eV, EI): *m/z* (%): 358 (14) [M^+], 302 (5) [$M^+ - 2\,CO$], 274 (100) [$M^+ - 3\,CO$]; IR (KBr): $\tilde{\nu} = 1959$ cm^{-1} (CO), 1876 (CO), 1661 (C=O), 1588 (C=C). **4d**: M.p. 68 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): $\delta = 5.64 - 5.84$ (m, 5H, CH), 6.21 (d, $^3J(H,H) = 16.0$ Hz, 1H; CH), 6.30 (d, $^3J(H,H) = 16.0$ Hz, 1H; CH), 7.21 (d, $^3J(H,H) = 16.1$ Hz, 1H; CH), 7.31 (d, $^3J(H,H) = 15.9$ Hz, 1H; CH), 7.33 – 7.83 (m, 5H; CH); ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C): $\delta = 94.19$ (CH), 95.46 (CH), 95.75 (CH), 101.76 (C_{quat}), 125.70 (CH), 126.49 (CH), 128.74 (CH), 129.18 (CH), 130.86 (CH), 134.72 (C_{quat}), 140.30 (CH), 143.65 (CH), 188.06 (C_{quat}), 233.45 (C_{quat}); MS (70 eV, EI): *m/z* (%): 370 (19) [M^+], 314 (15) [$M^+ - 2\,CO$], 286 (100) [$M^+ - 3\,CO$]; IR (KBr): $\tilde{\nu} = 1965$ cm^{-1}(CO), 1886 (CO), 1651 (C=O), 1618 (C=C).

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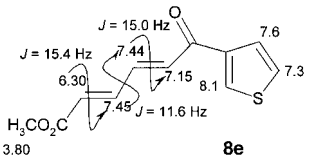

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Novel Water-Soluble Calix[4]arene Ligands with Phosphane-Containing Groups for Dual Functional Metal-Complex Catalysts: The Biphasic Hydroformylation of Water-Insoluble Olefins**

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The design and development of environmentally benign chemical processes has been the subject of growing attention, given the growing international consensus on green chemistry.[1] The Ruhrchemie – Rhône-Poulenc process[2] for the hydroformylation of propene, catalyzed by a water-soluble rhodium complex with triphenylphosphane trisulfonate (TPPTS, see Scheme 1) as a ligand, has been repeatedly discussed in the literature[3] because it allows the catalyst in the aqueous phase to be recycled by simple decantation, and the exclusive use of water as the reaction medium. However, its application is limited to olefins which have appreciable water solubility. To circumvent this problem, a variety of alternate strategies have been reported primarily for the hydroformylation of oct-1-ene. These include the addition of co-solvents,[4] promoter ligands,[5] or partially methylated β-cyclodextrins (β-CDs),[6] and the use of surface-active phosphanes,[7] thermoregulated phase-transfer catalysts,[8] or β-CD-modified diphosphanes[9] in place of TPPTS. None of these approaches have proved ideal, since all inevitably increase the difficulty of product separation[10] and, in addition for certain cases, a substantial decrease in activity takes place over consecutive catalytic cycles.

The approach described herein involves the use of novel water-soluble calix[4]arenes with phosphane-containing groups, named phosphacalix[4]arenes,[11] as ligands for dual functional metal-complex catalysts. Our hypothesis was that water-soluble phosphacalix[*n*]arene – metal complexes would function not only as homogeneous metal catalysts but also as inverse phase-transfer catalysts,[12, 13] which facilitate reactions

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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.

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