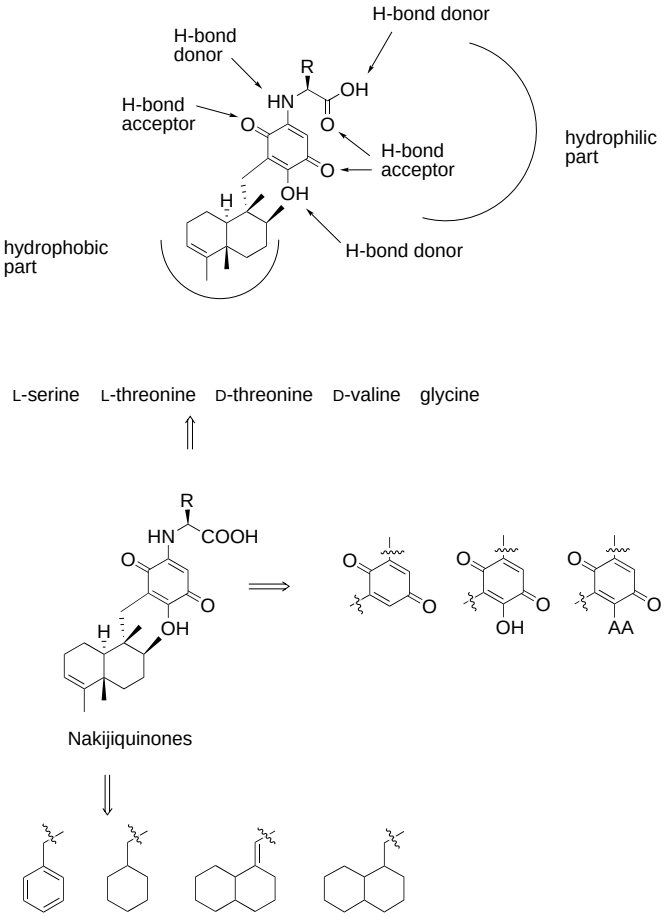
Natural Product Derived Receptor Tyrosine Kinase Inhibitors: Identification of IGF1R, Tie-2, and VEGFR-3 Inhibitors**

Petra Stahl, Lars Kissau, Ralph Mazitschek, Athanassios Giannis,* and Herbert Waldmann*

Angiogenesis, the development of new blood vessels from pre-existing ones, is central to wound repair, inflammation, and embryonic development. Furthermore, aberrant angiogenesis is considered to be a key step in tumor growth, spread, and metastasis.[1, 2] Vascular development depends on endothelium-specific receptor tyrosine kinases, in particular the vascular endothelial growth factor receptors 1–3 (VEGFR1–3) and the Tie-2 receptor.[3] All these receptors have been implicated in tumor angiogenesis,[4–8] and antagonization of Tie-2, VEGFR-2, or VEGF-D (a ligand of VEGFR-3) inhibits tumor growth and tumor metastasis in vivo.[7, 9, 10] The development of low molecular weight inhibitors of these receptor tyrosine kinases is among the most promising approaches to the development of new, alternative antitumor drugs, and several inhibitors of VEGFR-2 are in clinical trials.[11, 12] The combination of VEGFR-2 inhibitors with Tie-2 antagonists should potentiate their anti-angiogenic effects.[6] Furthermore, inhibitors of VEGFR-3 would suppress the metastasis of lymphogenic tumors. To date however, only a few cases of small-molecule inhibitors of the Tie-2 and VEGFR-3 receptors have been reported.[13] Herein we describe the identification of inhibitors of these proteins from a compound library that was derived from a natural product.

We have recently proposed a new concept for enhancing the process of finding lead compounds, by use of combinatorial methods.[14] The key principle of this concept is to employ natural products with known biological activity as biologically validated starting points in structural space, which are selected by evolution for binding to structurally conserved, yet genetically mobile protein domains. The frameworks of such natural products may then serve as a guiding principle for the development of relatively small compound libraries, which should yield significantly higher hit-rates than much larger libraries, designed exclusively on the basis of available and proven chemical transformations.

In the light of this concept, we synthesized a library of 56 nakijiquinone analogues (Scheme 1), the only natural products known to be inhibitors of the Her-2/Neu receptor tyrosine kinase,[15] and investigated these analogues as possible inhibitors of the receptor tyrosine kinases involved in angiogenesis.



Scheme 1. Structure of the nakijiquinones and plan for the synthesis of nakijiquinone analogues.

The design of the nakijiquinones analogues was based on the modular structure of the natural products. The nakijiquinones consist of a hydrophobic diterpene unit, which may interact with a hydrophobic pocket close to the ATP binding site,[12] a quinone-type building block, and an amino acid, the latter two of which may participate in hydrogen bonding to the ATP binding site of kinases. Consequently, the diterpene part was replaced with simple hydrophobic structures (Scheme 1). The hydrophilic amino acids serine and threonine, and the hydrophobic acids valine and glycine were chosen, and the stereochemistry was also varied. To modify the type and number of hydrogen-bond donors and acceptors, we introduced either one or two amino acids, an amino acid and an OH group, or only one amino acid.

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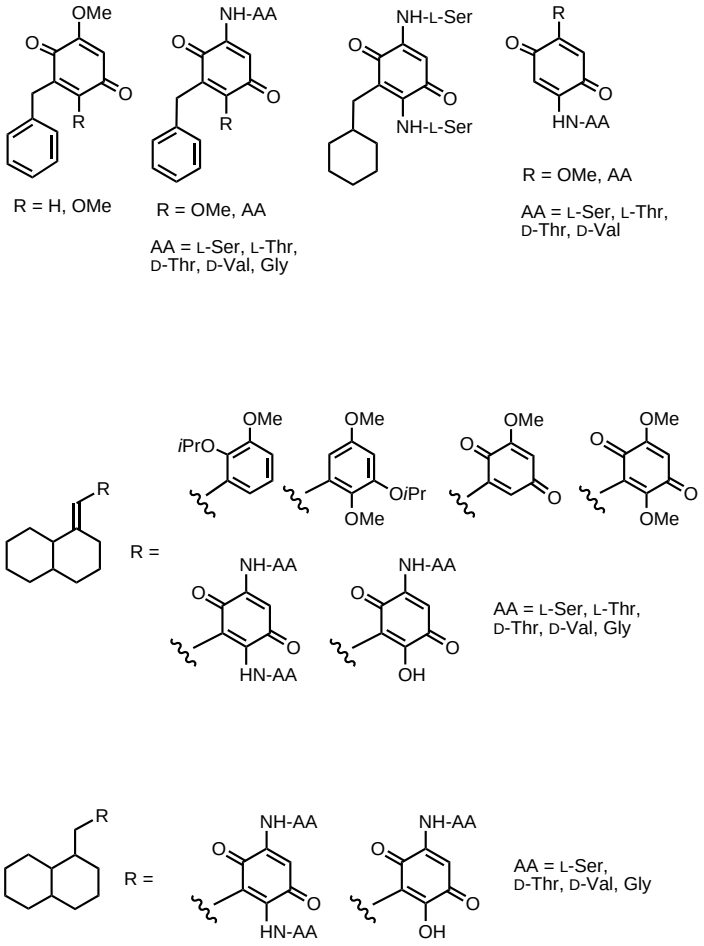
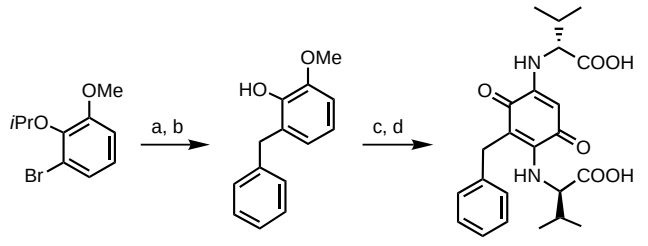
Scheme 2 shows the majority of the library members that were synthesized. A series of analogues was built up, in which the diterpene unit was replaced either by a benzyl group, a cyclohexane ring, a *n*-butyl group (structure not shown), or by



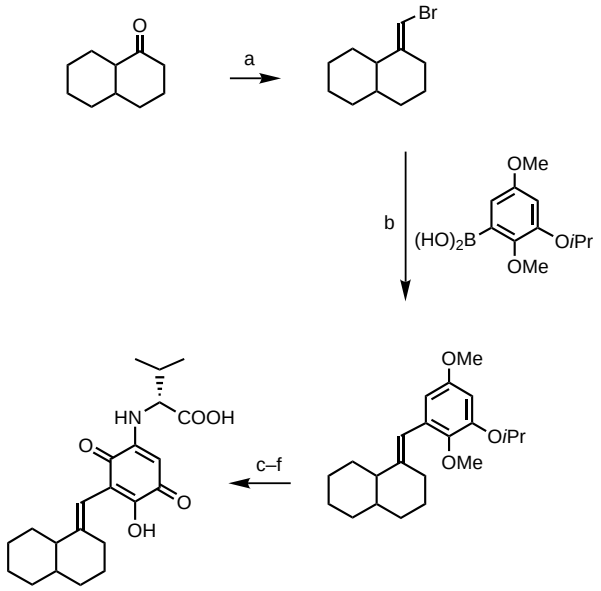
Scheme 2. Representative members of the nakijiquinone library.

a hydrogen atom. In general, these compounds were synthesized from appropriately substituted and selectively protected phenolic ethers, by means of a reaction sequence consisting of selective deprotection, oxidation to the quinoid system, and addition of an amino acid to the resulting vinylogous esters (by analogy to the methods described in the total synthesis of the nakijiquinones; a representative example is given in Scheme 3).[15]



Scheme 3. Synthesis of an amino acid substituted quinone. a) *n*BuLi, THF, −78 °C, 30 min, then CuI →40 °C; −78 °C, benzyl bromide, THF, 55 %; b) BCl_3, CH_2Cl_2, 0 °C, 88 %; c) O_2, N,N'-ethylenebis(salicylideneiminato)-cobalt(II)(salcomine), DMF, 70 %; d) D-valine, $NaHCO_3$, EtOH, 75 %.

The same aromatic building blocks and the oxygenation/amino acid introduction methodology were employed in the synthesis of analogues with a decalin system. Linkage to a *trans*-decalin building block with an exocyclic double bond was achieved by the Suzuki coupling of substituted arylboronic acids to the corresponding decalin-derived vinyl bromide (a representative example is given in Scheme 4). Reduction of the double bond in the Suzuki products yielded analogues with an alkyl side chain attached to the decalin core.



Scheme 4. Synthesis of a decalin analogue of the nakijiquinones. a) $BrCH_2PPh_3Br$, KO*t*Bu, THF, −78 °C →RT, 63%; b) $[Pd(PPh_3)_4]$, toluene, EtOH, Na_2CO_3, 90 °C, 24 h, 74 %; c) BCl_3, CH_2Cl_2, 0 °C, 89%; d) $ON(SO_3K)_2$, H_2O, benzene, aliquat 336, Na_2CO_3, 78 %; e) KOH, MeOH, H_2O, 59 %; f) D-valine, $NaHCO_3$, EtOH, 56%.

These syntheses gave access to a compound library with 56 members, which was screened for possible inhibitors against receptor tyrosine kinases, selected to cover a wide spectrum of biological activities.

To this end, in addition to VEGFR-2 (KDR, flk-1), VEGFR-3 (flt-4), and Tie-2, Her-2/Neu, epidermal growth factor receptor (EGFR; ErbB-1), ErbB-2, and insulin-like growth factor 1 receptor (IGF1R) were also chosen. The Her-2/Neu proto-oncogene belongs to the EGF family of receptor tyrosine kinases. It is over-expressed in approximately 30 % of all primary breast, ovary, and stomach cancers.[16] The EGFR, which is closely related to Her-2/Neu, has been implicated in human tumorigenesis, for example, of glioblastoma as well as in numerous tumors of epithelial origin including breast and oesophageal tumors.[17] The insulin-like growth factor 1 receptor affects cell mitogenesis, survival, transformation, and insulin-like activities by the binding of its ligands, IGF1 and IGF2. This receptor influences post natal growth physiology, and its activity has been associated with malignant disorders such as breast cancer.[18] The anti-apoptotic effect induced by the IGF1/IGF1R system correlates to the induction of chemoresistance in various tumors.[19]

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Out of the 56 compounds subjected to the kinase assay, five compounds displayed inhibitory activity in the low micromolar range. The library of the nakijiquinone analogues did not contain any inhibitor of Her-2/Neu, EGFR, ErbB-2, or VEGFR-2 which warranted further investigation. Remarkably, four of the compounds investigated turned out to be inhibitors of the Tie-2 receptor (Table 1). Two of these (entries 1 and 2) proved to be selective for this kinase; the other kinases in the assay were not significantly inhibited at concentrations of up to 70 μM. In the light of these findings, 14 close analogues of the nakijiquinones, as well as synthetic nakijiquinones A, C, and D,[15] were investigated as inhibitors of the kinases described above; however, no further inhibitor was found.

The most potent inhibitor identified in this study is bisthreonine derivative **3** (entry 3), which not only inhibits the Tie-2 receptor with an IC_{50} value of 5 μM, but also demonstrates a similar activity against VEGFR-3. These results indicate that **3** may be of interest in the inhibition of angiogenesis in general, and in the prevention of lymphangiogenesis in particular. Furthermore, the functionalization of the central six-membered ring with two amino acid residues suggests that improvements in activity and selectivity may be possible by variation of the amino acid residues.

The data given in Table 1 indicate that a quinoid system flanked by a hydrophobic group (entries 1 and 2) may be important for binding. Thus, the corresponding quinoid compound, analogous to **1** and **2** but lacking a further hydrophobic substituent, inhibits neither Tie-2 nor VEGFR-3. The presence of an amino acid as a vinylogous amide seems to enhance inhibitory activity, probably by providing a hydrogen-bond donor/hydrogen-bond acceptor motif. Notably, compound **4** inhibits the IGF1 receptor selectively with an IC_{50} value of 500 nM. The finding that this small nakijiquinone-analogue library yielded two IGF1R inhibtors indicates that this class of compounds in general may provide a suitable lead structure for the development of more potent IGF1R inhibitors.

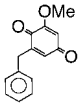
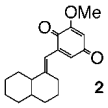
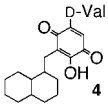
Detailed analysis of the inhibitory activity of **3** revealed that it is a competitive inhibitor and competes with ATP for the binding site of the nucleotide triphosphate. The K_i value and K_M values were found to be 3 μM and 19 μM, respectively (with ATP as the substrate).

To rationalize the selectivity displayed, for example, by compound **4**, which embodies a quinoid system and a hydrophobic annelated ring system and thereby closely resembles the nakijiquinones, the potential binding modes to Tie-2 were investigated by means of molecular modeling experiments. To this end, homology models were constructed for VEGFR-2, VEGFR-3, and Tie-2, which used the available crystal structures of FGFR-1 as templates (Figure 1).[12, 14, 20] Although an X-ray crystal structure of Tie-2 (apo-enzyme) has been reported,[21] it does not provide a suitable basis for modeling experiments as receptor tyrosine kinases are known to undergo significant conformational changes upon ligand binding.

The homology models of the Tie-2, VEGFR-2, and VEGFR-3 kinase domains were constructed by using CHARMM,[22] MODELLER,[23] WHATCHECK,[24] and WitnotP,[25] and employed the available crystal structures of the FGF receptor 1 as templates. The crystal structures of the FGF receptor 1 were chosen because of their good sequence agreement within the kinase domain with VEGFR-3 (≈51%), Tie-2 (≈45%), and VEGFR-2 (≈56%). These values are above the 30% minimum, usually considered to be the limit for a good homology model.[26] The primary alignment was performed by DIALIGN[27] and corrected manually. For the purpose of building the homology models, the residues of the kinase insert domain were deleted from the sequences.

The choice of orientation of the inhibitors within the ATP binding sites was guided by our previous work[15] and by the interactions described by Mohammadi et al.[20] After manual

Table 1. Inhibition of different receptor tyrosine kinases by nakijiquinone analogues.

Entry	Compound	IC_{50} for receptor [μM][a] EGFR	Her-2/Neu	ErbB-2	IGF1R	VEGFR-2	VEGFR-3	Tie-2
1	 **1**	–	–	–	–	–	–	18
2	 **2**	–	–	–	–	–	–	14
3	 **3**	–	–	–	6	–	3	5
4[b]	 **4**	–	–	–	0.5	–	–	9

[a] To assay the inhibitory activity, the kinase-catalyzed phosphorylation of poly(Glu-Tyr) in the presence of varying concentrations of inhibitor was determined. The kinases were employed as fusion proteins of glutathione-S-transferase (GST) and the respective kinase domain. The relative amount of phosphorylated substrate was quantified by means of an anti-phosphotyrosine enzyme-linked immunosorbent assay (ELISA), which employed an anti-phosphotyrosine antibody conjugated to horseradish peroxidase (POD). The bound antibody was detected by the light emission after addition of a chemiluminescence substrate for POD. [b] Compound **4** was investigated as an inseparable mixture of diastereomers.

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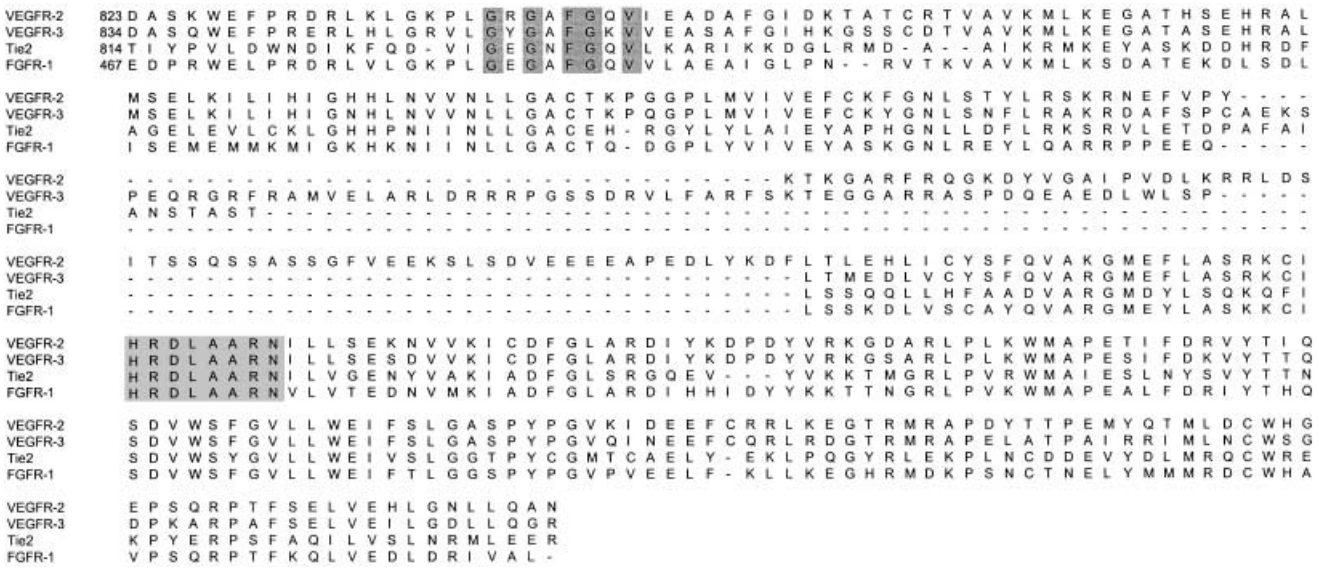

Figure 1. Alignment of amino acid sequences of VEGFR-2, VEGFR-3, Tie-2, and FGFR-1. The sequences were obtained from the Swiss – Prot database (VEGFR-2: P35968, VEGFR-3: P35916, Tie-2: Q02763, FGFR-1: P11362).

docking, the energy of the ligand – protein complex was minimized by using CHARMM.[22] According to these investigations, **4** binds in the mode shown in Figure 2. Compound **4** inhibits Tie-2 in the low micromolar range, but demonstrates

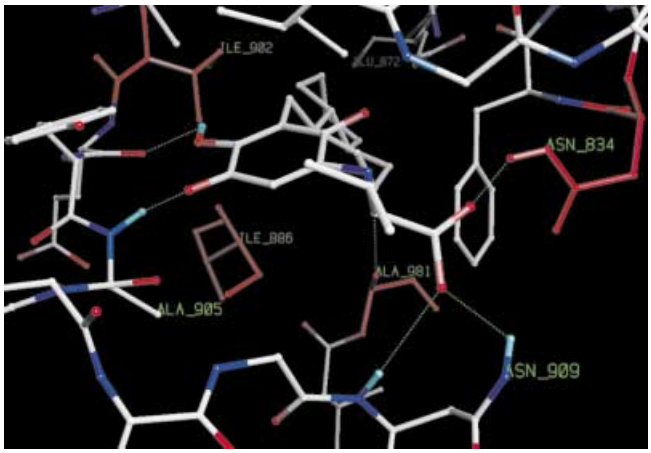

Figure 2. Proposed binding mode of compound **4** to the active site of Tie-2. Side chains that influence selectivity are colored red.

no activity towards VEGFR-2 or VEGFR-3. We attribute this selectivity to unfavorable interactions of the decalin moiety with C989 in VEGFR-2 (corresponds to C900 in VEGFR-3 and A981 in Tie-2) and to the formation of a hydrogen bond between the carboxy group of **4** and the amino acid N834 of Tie-2 (A844 in VEGFR-2 and A855 in VEGFR-3). Compound **4** binds in a manner in which the essential hydrogen bonds to the amino acids E917, C919, and N909 may be formed. Furthermore, amino acids I902 and I886 in Tie-2 cause the hydrophobic pocket in our model to be somewhat smaller than the pockets in VEGFR-2 and VEGFR-3. The decalin moiety of **4** covers the accessible surface in the hydrophobic pocket of Tie-2 much better than in VEGFR-2, where some space is left unoccupied.

We have shown that a relatively small library based on a naturally occurring kinase inhibitor yields potent inhibitors for other kinases with a high hit rate. This led to the identification of IGF1R, Tie-2, and VEGFR-3 inhibitors. These results may open up entirely new opportunities for the suppression of angiogenesis and lymphangiogenesis, and for the development of new anti-cancer drugs. Moreover, the results support our proposed concept for the enhancement of the hit and lead finding process.[14] The results show that to achieve high hit rates, the synthesis of natural product derived libraries is necessary to counterbalance the varying amino acid sequences found in repeatedly occurring protein domains with similar structures (here the kinase domains). The synthesis of the natural products alone would not have yielded the desired inhibitors.

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Selective Direct Synthesis of Organofunctionalized Dialkylgermanes from Solvochemically Activated Germanium**

Sabine Schlecht

Since the first successful experiments aimed at the direct synthesis of organosilanes and organogermanes, carried out by Rochow and Müller in 1942 – 1947,[1, 2] a whole industry for the production and application of alkylchlorosilanes has evolved. The direct synthesis of alkylgermanes, however, has received much less attention, although alkylated polygermylenes[3] and mixed polygermasilylenes,[4] the synthesis of which requires diorganogermanium compounds, have gained increasing importance as photoconducting polymers and photoresists. Their surface properties and their absorption maxima depend not only on the type of polymer backbone but also on the nature of the organic substituent on the diorganogermanium compound.[3, 4]

Like the direct synthesis of alkylchlorosilanes, the oxidative addition of alkyl halides to germanium is also clearly exothermic [Eqs. (1) – (3)].[5]

$$2\,CH_3Cl + Si \xrightarrow[300\,^\circ C]{Cu} (CH_3)_2SiCl_2 \qquad \Delta H_R = -304\ kJ\,mol^{-1}$$
$$2\,C_2H_5Cl + Si \xrightarrow[350\,^\circ C]{Cu} (C_2H_5)_2SiCl_2 \qquad (1)$$

$$2\,CH_3Cl + Ge \xrightarrow[320\,^\circ C]{Cu} (CH_3)_2GeCl_2 \qquad \Delta H_R = -97\ kJ\,mol^{-1} \qquad (2)$$

$$2\,CH_3Br + Si \xrightarrow[325\,^\circ C]{Cu} (CH_3)_2SiBr_2 \qquad \Delta H_R = -246\ kJ\,mol^{-1} \qquad (3)$$

Nonetheless, the direct reaction of alkyl halides with elemental silicon or germanium requires very drastic conditions (for the synthesis of an organoelement compound) and the use of a copper catalyst [Eqs. (1) – (3)]. This is due to the pronounced kinetic inertness of the elemental tetrels. The required reaction temperature of about 300 °C[5] prevents the use of functionalized organic halides in direct syntheses, because these compounds lack the necessary thermal stability. In the following, the application of solvochemically activated germanium in direct synthesis reactions is reported. When this very reactive form of germanium is used, the oxidative addition takes place at conditions mild enough to allow, for the first time, a direct synthesis of organofunctionalized germanes without the need for a copper-containing additive.

The solvochemical activation of germanium occurs through the reduction of its dichloride with a solution of $Li[Et_3BH]$ in THF[6] at room temperature [Eqs. (4) and (5)]. Completely X-ray amorphous, orange-colored germanium is obtained under these conditions.

$$GeCl_2 \cdot \text{dioxane} + 2\,Li[Et_3BH] \xrightarrow[RT]{THF} \underset{\text{orange}}{Ge^*} + 2\,LiCl + 2\,Et_3B + H_2 + \text{dioxane} \qquad (4)$$

$$GeI_2 + 2\,Li[Et_3BH] \xrightarrow[RT]{THF} \underset{\text{orange}}{Ge^*} + 2\,LiI + 2\,Et_3B + H_2 \qquad (5)$$

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