of chemically diverse alcohols (Figure 2). The mixture (1 mg mL^{-1} per alcohol) was analyzed by GC-FID as well as GC-MS. In the starting mixture all alcohols could be separated and identified by their mass spectra. Following treatment with resin **2** for 2 h, GC analysis revealed the complete disappearance of all of the alcohol precursors. All but one of the expected aldehyde, ketone, lactone, or dione products could be separated and identified; **8b** and **12b** co-eluted, whereas **16b** was not detected at all. The concentration of products with a low-boiling point eluting early in the GC was reduced, whereas the concentration of the high-boiling aldehydes and ketones remained stable in the complex mixture.

In summary, the reported polymer-bound oxoammonium reagent should be of great value in polymer-supported transformations in solution, in automated parallel synthesis operations, and in flow-through reactors in up-scaled production processes. Herein we have only considered the preformed oxoammonium salts as reactive species. The potential of the TEMPO–resin should, however, be exploitable as well as in situ generated oxoammonium salt, obtained by one of the available regeneration systems (e.g. Cu^{II}/O_2), in multiple phases, or by electrochemical means.

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[24] Experimental details: a) Preparation of TEMPO resin **1**. Sodium hydride (1.28 g, stabilized with paraffin oil, 60%, 32.1 mmol) was suspended in dry DMF (40 mL) in a 100 mL round-bottom flask. 2,2,6,6-Tetramethylpiperidine 1-oxyl (3.57 g, 20.7 mmol) was added slowly, the flask was sealed with a drying tube, and stirred for 3 h. Chloromethylated divinylbenzene (1%)/polystyrene (loading 1.07 mmol g^{-1}, 100–200 mesh, 2 g, 2.14 mmol) was added and the reaction was agitated for three days at room temperature. The resin was filtered and thoroughly washed with water, water/DMF (1/1), DMF, THF, CH_2Cl_2, and MeOH and dried in vacuo. Loading: 0.93 mmol g^{-1}. Chlorine content: 0.07%. b) Oxidation to oxoammonium resin **2** (Method C; Scheme 1). *N*-Chlorosuccinimide (6 equiv) was dissolved in CH_2Cl_2, 4 M HCl in dioxane was added (5 equiv). After 5 min the solution was added to resin **1** (1 equiv) swollen in dry CH_2Cl_2. Agitation for 15 min was followed by filtration of the resin and washing with dry CH_2Cl_2. Half-life time ($t_{1/2}$) of the activated form was about one week when stored in vacuo at 4 °C. c) Oxidation of alcohols. Alcohols **3a**–**22a** (1 equiv) were dissolved in dry CH_2Cl_2. Freshly prepared oxoammonium resin **2** (5 equiv as calculated from the loading of resin **1**) was added and agitated at room temperature for 1 h for the primary alcohols and 2 h for the secondary alcohols. The resin was filtered and washed with CH_2Cl_2, the washings were employed for analysis by GC, using a 25 m × 0.32 mm Permabond SE 54 ($d_f = 1.0\,\mu$) fused silica capillary. Temperature program: 50 °C, 2 min isotherm, 5 °C min^{-1} to 200 °C. H_2 was used as carrier gas (p_i = 50 kPa) for FI detection and He for GC-MS in the EI-mode (70 eV). Purities are reported in Table 1. Exemplified yields for 10 mg alcohol, after reaction for 1 h, washing with CH_2Cl_2 (4 × 3 mL), and evaporation of the solvent at room temperature: **9b:** 8.9 mg, 90%; **10b**: 8.7 mg, 88%; **20b:** 9.2 mg, 91%. The identity of the isolated products was confirmed by NMR analysis (250 MHz, $CDCl_3$).
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Thwarting β-Hydride Elimination: Capture of the Alkylpalladium Intermediate of an Asymmetric Intramolecular Heck Reaction**

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Dedicated to Professor Dieter Hoppe on the occasion of his 60th birthday

The asymmetric intramolecular Heck reaction[1, 2] has proven to be one of the most efficient methods for enantioselective construction of quaternary carbon centers.[3] We

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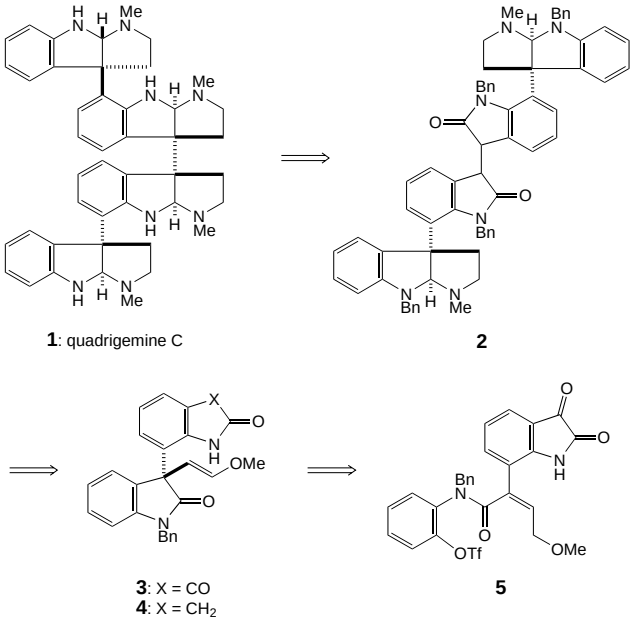
Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

have been engaged for some time in the development of catalytic asymmetric Heck cyclizations, with particular focus on enantioselective synthesis of oxindoles containing quaternary stereocenters.[4] Chiral oxindoles of this type have numerous applications in synthesis and are key intermediates in our approach to the synthesis of pyrrolidinoindoline alkaloids,[5] having recently been employed in enantioselective total syntheses of monomeric[6] and dimeric[7] members of this large family of natural products.

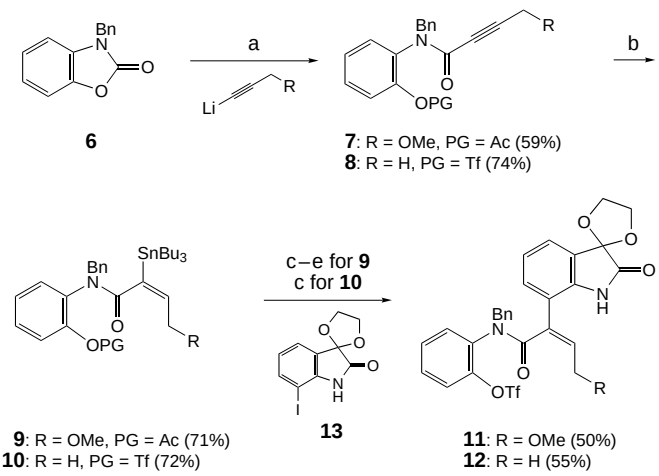
One focus of our current efforts is the enantioselective total synthesis of a tetrameric member of the polypyrrolidinoindoline alkaloid family, quadrigemine C (**1**),[8] which is proposed to have a *meso* bis(pyrrolidinoindoline) core decorated with two pyrrolidinoindolines of identical absolute configuration. This uncommon stereochemistry led us to consider a convergent dimerization strategy for synthesis of **1** (Scheme 1).



Scheme 1. Retrosynthetic analysis of quadrigemine C (**1**).

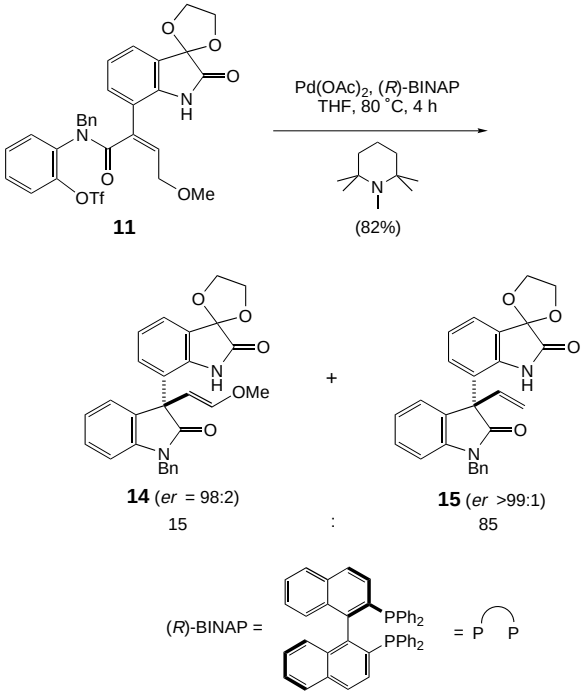
We envisioned dihydroisoindigo intermediate **2**, having both *outer* pyrrolidinoindoline units installed, a suitable substrate for our dialkylation method of constructing the vicinal stereogenic quaternary carbon centers of the central six rings.[9] Intermediate **2** should be accessible by aldol condensation of an isatin (**3**, X = CO) and a cognate oxindole (**4**, X = CH_2) followed by reduction. Enantioenriched isatin **3** and oxindole **4** in turn would derive from asymmetric Heck cyclization of triflate **5**.[10] Herein we report highly enantioselective Heck reactions of substrates of type **5** and the isolation of a σ-alkylpalladium intermediate having stereoelectronically accessible β-hydrogen atoms of this Heck sequence.[11]

Cyclization precursors **11** and **12** were each prepared from 3-benzyl-3*H*-benzooxazol-2-one (**6**)[12] in short routes analogous to those previously described (Scheme 2).[10] Stille coupling[13] of vinylstannane **9** or **10** with ketal-protected 7-iodoisatin **13**[14] and further functional group manipulation provided **11** and **12**.



Scheme 2. a) 1) lithium acetylide, THF, **6**, −78 °C to −25 °C, 5 h, 2) AcCl or $PhNTf_2$, THF, −25 °C to RT, 12 h; b) Bu_3SnH, $[Pd(PPh_3)_4]$, THF (BHT-inhibited), 0 °C to RT; c) $[Pd_2(dba)_3]\cdot CHCl_3$, P(2-furyl)$_3$, CuI, NMP, RT, 12 h; d) K_2CO_3, THF/MeOH (1:1), RT, 2 h; e) $PhNTf_2$, Cs_2CO_3, DMF, RT, 12 h. Ac = acetyl, BHT = 2,6-di-*tert*-butyl-4-methylphenol, Bn = benzyl, dba = *trans,trans*-dibenzylideneacetone, DMF = *N,N*-dimethylformamide, NMP = 1-methyl-2-pyrrolidinone, PG = protective group, Tf = trifluoromethanesulfonyl.

When triflate **11** was cyclized under conditions optimized in our earlier model study (40 mol% $Pd(OAc)_2$, 60 mol% (*R*)-BINAP, 1,2,2,6,6-pentamethylpiperidine (PMP), THF, 80 °C, 4 h),[10] two products were formed in an 85:15 ratio and 82% overall yield (Scheme 3). Only minor amounts of the expected Heck product **14** were isolated; the major product was **15**, a compound resulting from a β-methoxide, rather than β-hydride elimination. The structure of **15** was unambiguously secured by X-ray crystallography.[15] The quaternary carbon centers of both oxindoles **14** and **15** were formed in high



Scheme 3. Asymmetric Heck reaction of **11**.

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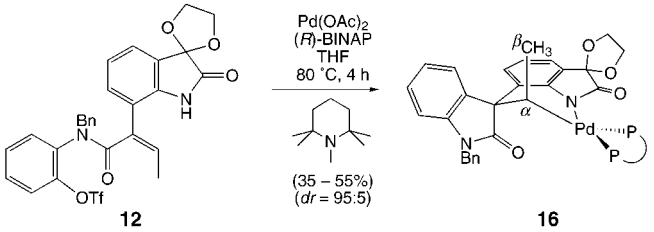
enantiomeric ratios ($er = 98{:}2$ and $> 99{:}1$, respectively).[16] O-Tosylation of the protected isatin fragment and X-ray analysis of the resulting *O*-tosylimidate derivative established the absolute configuration of **15**.[15, 17]

In an attempt to access **15** from a simpler precursor, we investigated the Heck cyclization of (*Z*)-butenanilide **12** (Scheme 4). To our surprise, the asymmetric Heck reaction



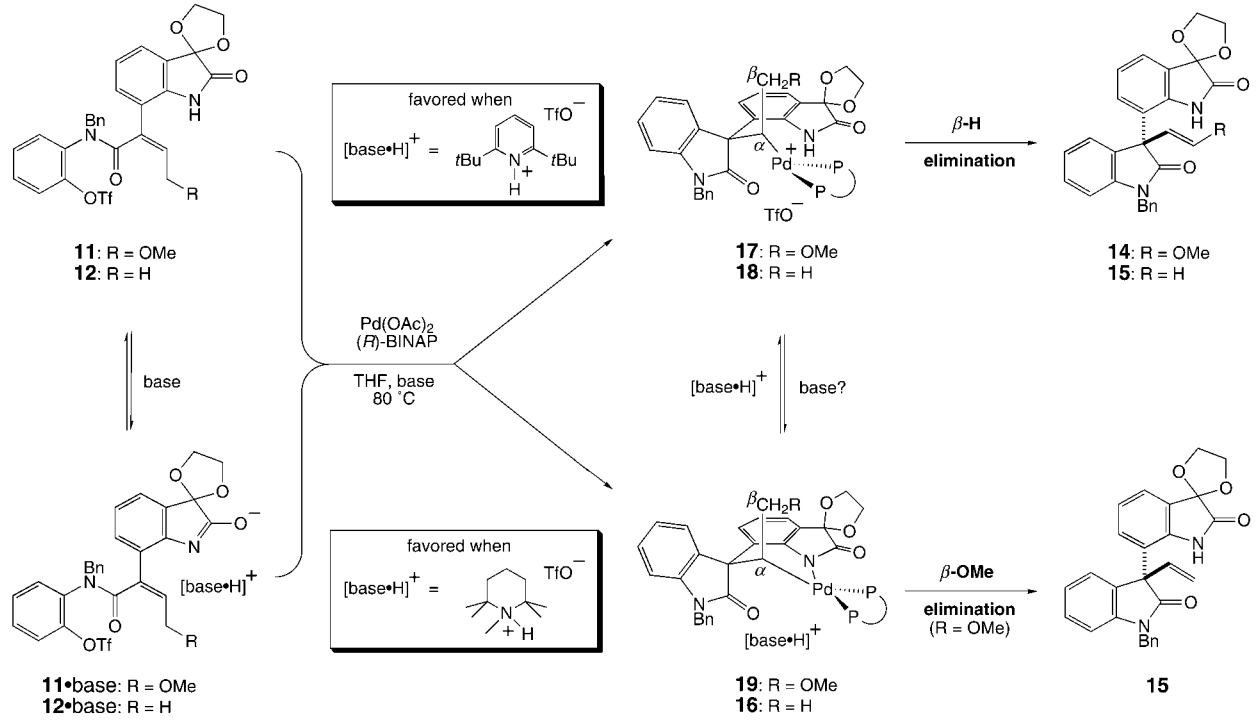
Scheme 4. Asymmetric Heck reaction of **12**. P⌒P = (*R*)-BINAP.

of **12** under identical conditions provided only traces of **15**, together with unreacted starting material and uncharacterized by-products. When **12** was cyclized in the presence of 100 mol % $Pd(OAc)_2$ and 150 mol % (*R*)-BINAP, substantial amounts (~35–55 % based on **12**) of a stable, palladium-containing compound **16** were isolated after workup and flash chromatography.

Careful mass spectrometric analysis and NMR studies support the structure depicted for **16** [$C_{27}H_{22}N_2O_4Pd \cdot$ (*R*)-BINAP] in Scheme 4. In particular, a $^{31}P-{}^{1}H$ correlation proves the existence of the relevant fragment of palladacycle **16**: both phosphorus atoms, P_{cis} and P_{trans}, couple with the hydrogen atoms attached to C_α and C_β; the individual coupling constants were resolved by decoupling experiments.[18a] The α-carbon has a diagnostic chemical shift of $\delta = 43.7$ in the ^{13}C NMR spectrum, which compares well with literature precedent for sp^3-hybridized alkylpalladium compounds.[19] The ^{31}P NMR spectrum with ^{1}H decoupling shows two sets of signals in a ratio of 95:5, which we assign as two epimeric palladacycles **16** and *epi*-**16**, indicating high stereoselection in forming the oxindole quaternary carbon center.[18b]

To provide further evidence for the structure of **16**, a pure sample of this product was heated in THF at 80 °C for 4 h in the presence of an excess of PMP, 2,6-di-*tert*-butylpyridine (TBP), or PMP hydrotriflate. Palladium complex **16** proved to be stable under these conditions, suffering only minor decomposition. In dramatic contrast, addition of an equimolar amount of the stronger acid, TBP hydrotriflate[20] to the bright yellow solution of **16** and THF at room temperature occasioned an instantaneous color change from yellow to red, indicating the generation of a Pd°–BINAP complex. After this solution had been heated at 80 °C for 4 h, the product of β-hydride elimination **15** was isolated in 48 % yield ($er = 95{:}5$). As suggested by this observation, replacing PMP with TBP in Heck reactions of **11** and **12** had a profound effect on the product distribution. Carrying out these reactions in the presence of TBP provided conventional Heck products arising from β-hydride elimination (**11** → **14** and **12** → **15**, Scheme 5) in good yield (Scheme 5), in contrast to related cyclizations employing PMP as a base (Scheme 3 and 4).[21]

Based on these observations, we propose that the reaction pathway of the Heck reactions of **11** and **12** is governed by the acidity of the conjugate acid of the trifluoromethanesulfonic acid scavenger employed. Although direct estimates do not exist for THF as solvent, TBP hydrotriflate should be a stronger acid than PMP hydrotriflate by about 7 pK_a units.[22, 23] When the Heck cyclizations are carried out in the



Scheme 5. Postulated mechanism for the formation of **14** and **15**.

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presence of the strong base PMP, palladacycles **16** and **19** are generated. Although **16** and **19** possess three and two β-hydrogen atoms, respectively, these intermediates do not undergo β-hydride elimination since a tightly bound ligand (BINAP or the conjugate base of the protected isatin) would have to dissociate to generate a vacant coordination site.[24, 25] Therefore, palladacycle **16** is stable, while **19** undergoes β-methoxide elimination to generate **15**.[26] In contrast, when the Heck reactions are carried out in the presence of the weaker base TBP, TBP hydrotriflate is acidic enough to shift the equilibrium from the palladacyclic intermediates toward the cationic palladium(II) species **17** and **18**, which undergo facile β-hydride elimination to generate conventional Heck products **14** and **15**.

In summary, an asymmetric Heck reaction has been successfully employed for the enantioselective construction ($er > 99{:}1$) of the quaternary stereocenter of an advanced intermediate en route to quadrigemine C (**1**). The unusual outcome of the Pd^0–BINAP-catalyzed cyclization of **11** is rationalized by the intermediacy of palladacycle **19**, which preferentially suffers β-methoxide elimination. The corresponding palladacyclic intermediate **16** lacking a methoxy group on the β-carbon atom is a stable compound. Palladacycle **16** is a rare example of a stable σ-alkylpalladium complex that has β-hydrogen atoms residing on a freely rotating β-carbon atom.[11] To the best of our knowledge, this is the first example of the isolation of an intermediate of this type in a Heck reaction.

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[16] HPLC analysis using a Daicel Chiralcel OD-H column (hexane/*i*PrOH 90:10) provided baseline resolution of enantiomers.

[17] Thus far attempts to chemically correlate **14** and **15** have failed. As a result, the absolute configuration of **14** is assigned on the basis of its similar HPLC characteristics on a chiral stationary phase to **15**,[16] and by analogy to our earlier model studies.[10]

[18] a) The full set of data is provided in the Supporting Information and copies of NMR specta are available from the authors. b) The ^{31}P NMR spectrum with ^{1}H decoupling with signals being assigned is depicted in the Supporting Information.

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[21] Reactions in the presence of TBP were not completed within 4 h. After 4 h, **11** gave **14** in 40% yield (40 mol% catalyst loading) and **12** provided **15** in 75% yield (100 mol% catalyst loading).

[22] The pK_a values for the conjugate acids of PMP (pK_a (50% aqueous ethanol) = 9.54[23a] and pK_a (acetonitrile) = 18.7[23b]) and TBP (pK_a (50% aqueous ethanol) = 2.70[23a] and pK_a (acetonitrile) = 11.8[23c]) have been measured in aqueous ethanol and estimated in acetonitrile; ΔpK_a is about 7 pK_a units in both solvents.

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