The enantioselective version of palladium-catalyzed allylic substitution, sometimes referred to as AAA (asymmetric allylic alkylation), has emerged as a powerful synthetic tool.[1] Since the first report of a stoichiometric AAA reaction in the 1970s,[2] it took almost 20 years of research until effective catalytic systems based on chiral ligands were developed. The major challenge in conducting such reactions enantioselectively arises from the fact that both the departure of the allylic leaving group, resulting in the formation of a cationic \( \pi \)-allyl–Pd complex and, in most cases, the attack of the nucleophile occur on the \( \pi \) face of the substrate opposite to the metal. Asymmetric induction therefore proceeds remote to the employed chiral ligands. However, some particularly successful concepts to address this issue have been devised, and over 100 catalysts have been developed.[3]

Besides high levels of asymmetric induction, advantages of the AAA methodology are a broad tolerance towards functional groups and, in contrast to many other catalytic asymmetric methods, a great flexibility in the bond type to be formed. For instance, H, O, N, S, P, and C nucleophiles can be employed. Among the many new opportunities thus arising for the synthetic chemist,[4] AAA reactions of cyclic substrates of type 1 and 2 have recently proven to be of particular value as they lead to novel and highly efficient strategies in the total synthesis of natural products. The abundance of the corresponding cyclic subunits in natural products together with the inherent potential in controlling the stereochemistry of cyclic scaffolds in the course of a synthesis makes these building blocks very attractive.

The reactions of meso compounds 1 and those of chiral cyclohexenes 2 with allylic leaving groups \( X \) differ in the nature of the enantiodiscriminating step (pathways A and B, respectively, in Scheme 1). In the substitution of meso compounds of type 1 (path A), the formation of the intermediate \( \eta^1-\pi\)-allyl–metal complex (ionization) constitutes the enantiodiscriminating step. The nucleophile is then introduced at the least-hindered allyl terminus with overall retention of configuration. Following path B, substrates of type 2 can be employed as racemic mixtures. With
the formation of the π-allyl complex, the stereochemical information of the substrate is lost and in this case the attack of the nucleophile from the face opposite to the metal represents the enantiodiscriminating step. According to Trost, this deracemization process can be regarded as a DYKAT (dynamic kinetic asymmetric transformation). Both pathways allow the selective induction of chirality and make up the starting point of some very efficient natural product syntheses published recently.

In a synthesis of epi-hygromycin A (Scheme 2) Trost et al. made use of four Pd-catalyzed allylic-substitution reactions employing versatile diphosphane bisamide ligands of type 3 in all cases. As a result of a larger bite angle of the phosphane groups, these ligands are believed to envelop the allylic system. The reaction of the meso-dihydrofuran 4 with the nucleophile 5 as an acyl anion equivalent afforded the monosubstitution product 6 in excellent yield and enantioselectivity (93% ee). The second allylic substitution was carried out with the ligand ent-3. Although a chiral ligand is not necessary in this case, a higher reactivity was observed. Moreover, the phenolic glycoside 10 was formed with perfect cis diastereoselectivity, in contrast to a previous synthesis in which the glycosylation step led to an anomeric mixture. The subsequent steps in the synthesis of 10 involved dihydroxylation of the double bond, Horner–Wadsworth–Emmons olefination, and attachment of the aminocyclitol moiety 9.

The synthesis of the aminocyclitol building block 9 (Scheme 3) started from the readily available racemic conduritol tetraester rac-11. In a remarkable twofold asymmetric allylic substitution process, both enantiomers were converted into the same bisbenzoate 15 by employing the chiral ligand 3. The ionization of the tetraesters 11 and ent-11 proceeded with different reaction rates, allowing the use of two different matched ligands 3 and ent-3. The ionization of the tetraesters 11 and ent-11 proceeded with different reaction rates, allowing the use of two different matched ligands. Therefore, only one chirality was introduced in the first step, which was subsequently transferred to the remaining acyclic fragments by enantioselective Wittig olefination with the same bisbenzoate 15.
rates, representing matched and mismatched cases, respectively. With the tetraacetate rac-11 (R = Ac) a nearly perfect kinetic resolution was observed and only 50% (i.e. the enantiomer 11) of the starting material was converted. When the leaving group was changed from an acetate to a more reactive alkyl carbonate, both enantiomers were rapidly converted into complex 12. Attack of the benzoate nucleophile led initially to the enantiomerically pure monosubstitution product 13 (R = CO₂CH₂CCl₃), which still bears an allylic leaving group (with the same configuration as in the matched substrate 11). A second substitution then gave rise to conduritol tetraacetate 15 (> 99% ee). Reductive cleavage of the carbonate groups R and desymmetrization by derivatization of one of the homotopic hydroxy groups was followed by five further steps to yield the required aminocyclitol derivative 9.

Notably, the straightforward strategy used for the synthesis of the glycoside part of epi-hygroycin A was not based on a sugar-derived starting material from the chiral pool. Instead, the meso compound 4 was used, which is not suited for common enzymatic desymmetrization methods.

AAA reactions also provide easy access to chiral nitrogen-substituted cyclopentene derivatives, which may serve as building blocks for the synthesis of alkaloids, as demonstrated by Blechert and co-workers. In a recent synthesis of (−)-swainsonine (22, Scheme 4) the key intermediate 17 was prepared by an intramolecular substitution of one of the enantiotopic carbamate groups of 16.[6a] As demonstrated earlier, ligand 3 gives excellent ee in this transformation if NEt₃ is used as a base.[6b] The cyclization product 17 already contains the two vicinal stereocenters found in (−)-swainsonine (22). Upon treatment of the allyltosylamide 18 with the Grubbs catalyst under an atmosphere of ethylene, a remarkable ring-opening/ring-closing-metathesis cascade took place. In the reaction, the oxygen-bearing stereocenter was transferred to the side chain of the newly formed dihydropyrrole 19. Only a few more steps were required to set up the indolizidine framework, and the synthesis was completed by dihydroxylation and deprotection. In the synthesis of (−)-juvabione (31) by Bergner and Helmchen (Scheme 5), two Pd-catalyzed allylic substitutions were used to attach the side chains onto the cyclohexene ring.[7] At first, asymmetric alkylation of cyclohexenylacetate (rac-24) with lithium dimethyl malonate in the presence of ligand 23 afforded 25 in 91% yield with 95% ee. After a sequence of Krapcho decarbomethoxylation, saponification, iodolactonization, and dehydrohalogenation, the enantiomerically pure key intermediate 26 was obtained, which was also used in the synthesis of (−)-wine lactone.[7b] Fully diastereoselective α-methylation afforded the lactone 27 in which the C=C bond is favorably positioned for a second allylic substitution. The 2-acloyxymalonate 28 was used as a formyl anion equivalent in the second Pd-catalyzed alkylation, which proceeded with complete regio- and diastereoselectivity to give 29. The final part of the synthesis was initiated by reduction and glycol cleavage to liberate the masked carboxy group. This was followed by methylation and isomerization of the double bond to yield 30, which was finally converted into (−)-juvabione (31) in three steps.

Recently it was demonstrated by Mori et al. that the use of N-sulfonated ortho-bromoaniline as a nucleophile in an AAA process of type B paved the way for a simple assembly of optically active indoles by means of a Heck cyclization. On this basis, a new strategy for the synthesis of Strychnos alkaloids was devised and demonstrated in the synthesis of (−)-dehydrotubifoline (42) and (−)-tubifoline (Scheme 6).[8] In the first step, the Pd-catalyzed reaction of the cyclohexene rac-34 with the anilide 33 in the presence of (S)-binapo (32) as a chiral ligand yielded the building block 35 in 84% ee. After recrystallization enantiomerically pure 35 was obtained. A nitrile group was introduced and Heck cyclization of 36 gave rise to the...
annulated indoline 37, in which the crucial quaternary stereocenter had been installed. This delivered the cyclohexene double bond in the correct position for the cyclization of 38 to 39 through Pd-mediated allylic oxidation. The double bond was shifted further by one position in a four-step sequence to set the stage for the final Heck cyclization. After removal of the N-protecting groups and alkylation of the more reactive pyrrolidine nitrogen atom with a iododalkene C4-unit (41), a Heck reaction directly afforded the target compound 42. The synthesis is characterized by the fact that all cyclizations are performed in a fully diastereoselective manner using Pd-catalyzed reactions and that the absolute stereochemical information was established in the initial AAA reaction.

In a spectacular synthesis of (−)-codeine (53) and (−)-morphine (54, Scheme 7) Trost and Tang followed a related general strategy for the stereocontrolled construction of a complex cyclic framework around a cyclohexane ring.[9] Asymmetric allylic substitution of rac-44 with the functionalized phenol 43 afforded the key intermediate 46 (87% ee). The enantiomeric purity was enhanced to 96% ee by recrystallization at the stage of the homologous nitrile 47. In an intramolecular Heck reaction, the second (quaternary) stereocenter was established with complete diastereoselectivity. The product 48 also served as an intermediate in the total synthesis of (−)-galanthamine.[9b] For the synthesis of morphine, the common intermediate 48 was first converted into the bromoalkene (Z)-49 before a second Heck cyclization was used to build up the phenanthrene scaffold with a correctly placed double bond. Allylic oxidation of 50 (SeO2, then Dess–Martin periodinane reagent) followed by diastereoselective reduction with DIBAH (diisobutylaluminum hydride) gave the alcohol 51, which was then converted into the secondary amine 52. The final cyclization by means of a photochemically induced intramolecular hydrazinomation yielded (−)-codeine (53, R = Me), from which (−)-morphine (54, R = H) was prepared by a known protocol. A noteworthy feature of this latest synthesis of

| Scheme 5. Synthesis of (−)-juvabione by Helmchen and Bergner. dppe = 1,2-Bis(diphenylphosphanyl)ethane. |
The prominent target molecule morphine is the masterly use of the double bond in the pivotal cyclohexene ring to serve as a platform for three successive Pd-catalyzed transformations.[10]

The few selected examples discussed herein show only a facet of the synthetic scope of asymmetric allylic substitution. Besides the manifold options for further transformation of the double bond of the AAA reaction products, the true synthetic power arises from the variety of functionalized building blocks that can be enantioselectively joined in a convergent manner.


