High stereoselectivity in chelation-controlled intermolecular Heck reactions with aryl chlorides, vinyl chlorides and vinyl triflates[†]

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Highly stereoselective chelation-controlled Pd(0)-catalyzed β -arylations and β -vinylations of a five-membered chiral, pyrrolidine-based vinyl ether were achieved using aryl- and vinyl chlorides as substrates, yielding quaternary 2-aryl/vinyl-2-methyl cyclopentanones in 89–96% ee under neutral reaction conditions.

The Heck vinylic substitution reaction is a mild palladiumcatalyzed reaction which has found a wide range of applications in organic synthesis.^{1,2} As a unique carbon-carbon bond forming process,³ this arylation/vinvlation of an olefin holds even greater synthetic potential provided that the stereochemical outcome can be fully dictated. With cyclic olefins, control of the stereochemistry can be achieved either by employing a homogeneous catalytic system with chiral bidentate ligands⁴ or, alternatively, by relying on substrate-bound, removable, catalyst directing groups.⁵ On the other side, the use of rarely commercially available organic triflates or expensive iodides has proven essential, limiting the applicability of this methodology. Less reactive aryl- and vinyl chlorides are, however, both more easily accessible and less expensive alternative organopalladium precursors. In the case of achiral Heck reactions, noteworthy advances with aryl chlorides have been described by the groups of Milstein⁶, Fu⁷ and Beller⁸, among others.⁹ To the best of our knowledge, neither intra- nor intermolecular Heck reactions with high chiral control have been reported utilizing organic chlorides as substrates. In this paper we establish that in the presence of highly active Pd(t-Bu₃P)₂ catalyst⁹ and using standard neutral reaction conditions,² the Heck reaction with tetrasubstituted vinyl ether 1a and organic chlorides 2a-k can indeed be achieved in excellent diastereoselectivities, furnishing the 2,2-difunctionalized cyclopentanone products 4a-k in 89-96% ee after hydrolysis (Scheme 1).

The use of alkenes carrying a metal-coordinating amino group has been reported by several groups, including ours, as a fruitful strategy to overcome the reluctance of substituted alkenes to participate in intermolecular Heck reactions and to control the stereoselectivity of the process.^{5,10,11} Vinyl ethers **1a,b** were prepared as previously described¹² and vinyl ethers **1c,d** were synthesized *via* a similar acid-catalyzed transacetalization–elimination process (Scheme 2). Despite extensive chromatography, **1c** was obtained in only 90% purity (**1c** : **1d** = 90 : 10). In order to evaluate aryl chlorides as coupling partners in asymmetric transformations, we decided to investigate **1a–d** as olefins equipped with a strongly



Pd(II)-coordinating (S)-N-methylpyrrolidine catalyst directing group¹³ suitable for selective arylations at elevated temperatures. In an earlier report, vinyl ether **1a** was arylated with 7 different aryl iodides and 2 different aryl bromides, yielding 2-aryl-2-methyl-cyclopentanones **4** in 45–78% yields and 90–98% ee.¹²

A first coupling of **1a** (1.0 equiv) with aryl chloride **2b** (1.3 equiv) using standard neutral reaction conditions in the presence of LiCl (2.0 equiv), NaOAc (1.2 equiv), K₂CO₃ (1.2 equiv) and 5.0 mol% of Pd(*t*-Bu₃P)₂ in 2.2 mL of aqueous DMF (10% water), gave full conversion after 18 h of oil-bath heating at 100 °C. The formed β -arylated Heck product **3b** was isolated in 51% yield after careful flash chromatography in the presence of Et₃N, showing an excellent diastereomeric purity by ¹H NMR (Scheme 3). The synthesis of **3b** was repeated and after complete conversion of **1a** based on GC-MS, a convenient acidic hydrolysis directly provided the enantiomerically enriched 2-methyl-2-tolyl cyclopentanone **4b** in 57% yield and 91% ee as determined by chiral HPLC. Lower catalyst loadings of 1.5 mol% and 3.0 mol% in the model reaction between **1a** and **2b** resulted in incomplete conversion of starting





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Entry	Aryl chloride		Time	Isolated yield ^a	ee ^b	$[a]_{\rm D}^{23}$
1	Me ₂ N	2a	9 h	68 (%) 4a	94 (%)	+39°
2	-CI	2b	18 h	57 (%) 4b	91 (%)	+86°
3	CI-CI	2c	20 h	55 (%) 4c	90 (%)	+58°
4	CI-CI	2d	11 h	60 (%) 4d	94 (%)	+52°
5	C	2e	12 h	59 (%) 4e	91 (%)	+79°
6	° — CI	2f	8 h	69 (%) 4f	93 (%)	+12°
7	°→−⊂I	2g	8 h	67 (%) 4g	92 (%)	+12°
8	Ph CI	2h	8 h	60 (%) 4h	96 (%)	+46°
9	N≡−√−CI	2i	8 h	65 (%) 4i	92 (%)	+44°

Table 1Stereoselective arylation of 1a with aryl chlorides and subsequent
hydrolysis

^{*a*} The reactions were performed at 100 °C under air with **1a** (0.15 mmol) as the yield determining substrate using standard neutral conditions. Ketones were obtained after hydrolysis with concentrated HCl (aq). Isolated yields are average of three runs. Purity >95% by GC-MS. ^{*b*} Ee of (+) isomer of **4** by chiral HPLC (average of three runs).

materials. To demonstrate the scope and applicability of this twostep, one-pot methodology, eight additional reactions were carried out with **1a**. Decent yields and excellent enantiomeric purities (90– 96% ee) were obtained for (+)-(R)-**4a**-**i**, including electron-rich, electron-poor, and *ortho*-functionalized aryl chlorides after 8–20 h of oil-bath heating (Table 1, entries 1–9). Competing hydrolysis of **1a** explains the somewhat moderate yields of **4a**-**i**. A test arylation of **1b** provided only a small amount of epimeric product. Unfortunately, both olefins **1c** and **1d** failed to participate in useful arylation reactions under the same standard neutral conditions for 24 h at 100 °C and 120 °C.

In order to accelerate the reaction rate, selected experiments were also carried out in sealed vessels under controlled microwave irradiation using the identical neutral reaction conditions as in the classical protocol but at higher temperature (Table 2).¹⁴ Full conversion of **1a** and similar yields as with classic heating could be obtained with the investigated four aryl chlorides after only 1–1.5 h of irradiation time at 140 °C. Disappointingly, with this high temperature methodology the enantioselectivities of isolated quaternary ketones **4b,d,f,g** were reduced to 84–89%.

Pioneering research by the Overman¹⁵ and Shibasaki⁴ groups has proven that vinyl triflates can be useful in intramolecular asymmetric Heck reactions to produce tetra-substituted carbon-centers. Thus to further explore the reactivity scope of **1a**, we decided to study two vinyl chlorides (**2j**,**k**) and two vinyl triflates (**2l**,**m**) as cyclic and acyclic coupling partners (Table 3). Surprisingly, vinyl triflates **2l**,**m** were more sluggish than the corresponding chlorides

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Entry	Aryl chloride		Time	Isolated yield ^a	ee ^b
1	-CI	2b	1.5 h	50 (%) 4b	84 (%)
2	CI-CI	2d	1 h	54 (%) 4d	88 (%)
3	°→−CI	2f	1 h	62 (%) 4f	85 (%)
4	°→−CI	2g	1 h	63 (%) 4g	89 (%)

^{*a*} The reactions were performed at 140 °C under air with **1a** (0.15 mmol) as the yield determining substrate using standard neutral conditions. Ketones were obtained after hydrolysis with concentrated HCl (aq). Isolated yields are average of three runs. Purity >95% by GC-MS. ^{*b*} Ee of (+) isomer of **4** by chiral HPLC (average of three runs).

 $\label{eq:transform} \begin{array}{ll} \textbf{Table 3} & \textbf{Stereoselective vinylation of 1a with vinyl chlorides/triflates and subsequent hydrolysis} \end{array}$

Entry	Vinyl-Cl/OTf		Time	Isolated yield ^a	ee ^b	$[a]_{\rm D}^{23}$
1		2j	15 h	60 (%) 4j	90 (%)	+11°
2	CI CI CI	2k	18 h	61 (%) 4k	90 (%)	+15°
3		21	22 h	58 (%) 4j	89 (%)	+10°
4	OTf	2m	24 h	59 (%) 4 k	90 (%)	+15°

^{*a*} The reactions were performed at 100 °C under air with **1a** (0.15 mmol) as the yield determining substrate using standard neutral conditions. Ketones were obtained after hydrolysis with concentrated HCl (aq). Isolated yields are average of three runs. Purity >95% by GC-MS. ^{*b*} Ee of (+) isomer of **4** by chiral HPLC (average of three runs).

2j,k employing identical standard neutral reaction conditions as in Table 1. As evident from Table 3, comparable yields (58– 61%) and very high enantioselectivities (89–90% ee) of isolated 2-methyl-2-vinyl ketones **4j,k** were, regardless of the choice of leaving group, realized after HCl-mediated hydrolysis. Analogous vinylation reactions with cyclohexene derivatives **1c–d** did not lead to any product.

After the successful use of vinyl triflates in stereoselective vinylations of **1a**, we decided to investigate readily available aryl triflates under identical standard neutral reaction conditions. However, no arylation of **1a** was observed using 4-CN-phenyl (**2n**), phenyl, 1-naphthyl and 4-tolyl triflates. To understand the reactivity pattern of aryl triflates with **1a**, we further investigated cationic reaction conditions¹⁶ employing **2n** as the arylating agent in the absence of a halide additive (Scheme 4). Interestingly, arylation of **1a** (1.0 equiv) with aryl triflate **2n** (2.0 equiv) using cationic reaction conditions in the presence of Et₃N (4.0 equiv), 6.0 mol% of Pd(OAc)₂ and 12.0 mol% of PPh₃ in 2.0 mL of DMF was productive. The arylation of **1a** was monitored by GC-MS analysis and after complete consumption of **1a** the Heck product



Scheme 4

3i was hydrolysed to **4i** in 63% yield and 88% ee. The rate of the reaction with **1a** and **2n** under cationic conditions (Scheme 4) was slower compared to the arylation rate using 4-CN-phenyl chloride (**2i**) under standard neutral conditions (Table 1, entry 9). Phenyl, 1-naphthyl and 4-tolyl triflates did not produce the desired arylation under the same cationic conditions.

In the substrate controlled arylation/vinylation of 1a using 2am and LiCl addition, the reaction route proceeding via the neutral π -complex as depicted in Scheme 1 appears reasonable. This chelation-controlled Heck pathway was previously suggested for the reaction of 1a with aryl iodides¹² and the only differences comprise the initial involvement of a T-shaped oxidative addition intermediate using the t-Bu₃P ligand,¹⁷ instead of the tetra-substituted 16-electron square planar palladium complex produced with less bulky ligands. Recently published DFT calculations¹⁸ predict chelation-controlled Si-face insertion of the neutral intermediate PhPdCl complex into the 1a vinyl ether double bond, furnishing R-configuration of the new quaternary center. This theoretical result was fully supported by optical rotation measurements of isolated ketone products 4 (Table 1).12 An explanation for the lack of reactivity in the coupling between 1a and phenyl, 1-naphthyl and 4-tolyl triflates could be the generation of a stable, chelated σ- or π-complex due to strong Pd(II)–N coordination.¹³ The low Heck-reactivity of six-membered, tetra-substituted olefins 1c-d was perhaps not surprising in the light of the reported slow arylation rate of dihydropyran using chiral P, N-ligands.¹⁹

In summary, highly stereoselective Pd(0)-catalyzed β -arylation and β -vinylation of a fully substituted cyclopentenyl vinyl ether has been achieved by employing a chiral, pyrrolidine-based and substrate-bound palladium(II)-directing group under neutral reaction conditions. This presents the first case of aryl- and vinyl chlorides being successfully utilized in asymmetric Heck reactions. Formed Heck arylation products were hydrolysed and isolated as the corresponding quaternary 2-aryl-2-methyl cyclopentanones in good to moderate two-step yields with excellent stereoselectivities (90–96% ee). Moreover, with high-density microwave-heating, the reaction times were reduced from many hours down to 1– 1.5 hour. The scope of the protocol was further increased to include vinyl triflates under neutral reaction conditions and one aryl triflate carrying a strongly electron-withdrawing *para*-cyano substituent under cationic conditions. We believe that this method should provide an attractive complement to direct Pd(0)-catalyzed α -arylation protocols,^{20–22} particularly when the use of organic chlorides and mild reaction conditions are of importance.

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