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

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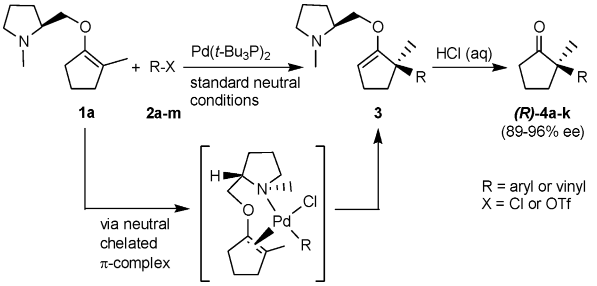
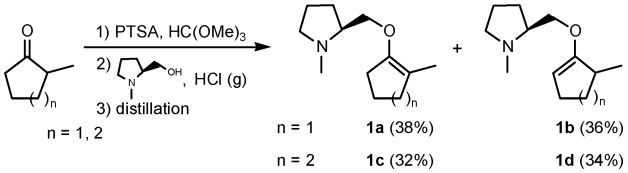
Highly stereoselective chelation-controlled Pd(0)-catalyzed β-arylations and β-vinylations of a five-membered chiral, pyrrolidine-based vinyl ether were achieved using aryl- and vinyl chlorides as substrates, yielding quaternary 2-aryl/vinyl-2-methyl cyclopentanones in 89–96% ee under neutral reaction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

The Heck vinylic substitution reaction is a mild palladium-catalyzed 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/vinylation 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 ligands[4] 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 Milstein[6], Fu[7] and Beller[8], 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-Bu$_3$P)$_2$ catalyst[9] 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 described[12] 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 group[13] 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]

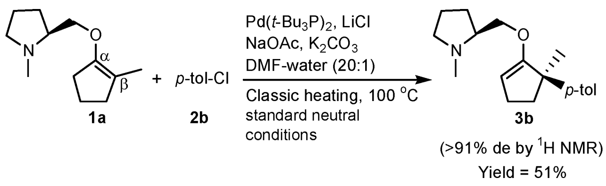


Scheme 1



Scheme 2

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), K$_2$CO$_3$ (1.2 equiv) and 5.0 mol% of Pd(t-Bu$_3$P)$_2$ 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 Et$_3$N, showing an excellent diastereomeric purity by ^{1}H 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



Scheme 3

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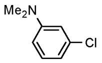
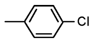
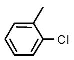
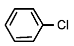
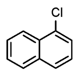
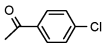
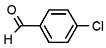
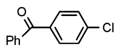
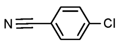
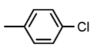
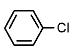
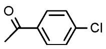
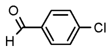
Table 1 Stereoselective arylation of **1a** with aryl chlorides and subsequent hydrolysis

Entry	Aryl chloride		Time	Isolated yield[a]	ee[b]	$[\alpha]_D^{23}$
1		**2a**	9 h	68 (%) **4a**	94 (%)	+39°
2		**2b**	18 h	57 (%) **4b**	91 (%)	+86°
3		**2c**	20 h	55 (%) **4c**	90 (%)	+58°
4		**2d**	11 h	60 (%) **4d**	94 (%)	+52°
5		**2e**	12 h	59 (%) **4e**	91 (%)	+79°
6		**2f**	8 h	69 (%) **4f**	93 (%)	+12°
7		**2g**	8 h	67 (%) **4g**	92 (%)	+12°
8		**2h**	8 h	60 (%) **4h**	96 (%)	+46°
9		**2i**	8 h	65 (%) **4i**	92 (%)	+44°

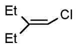
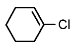
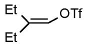
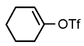
[a] The reactions were performed at 100 °C under air with **1a** (0.15 mmol) as the yield determining substrate using standard neutral conditions. Ketones were obtained after hydrolysis with concentrated HCl (aq). Isolated yields are average of three runs. Purity >95% by GC-MS. [b] Ee of (+) isomer of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

Table 2 Microwave-accelerated arylation of **1a** with aryl chlorides and subsequent hydrolysis

Entry	Aryl chloride		Time	Isolated yield[a]	ee[b]
1		**2b**	1.5 h	50 (%) **4b**	84 (%)
2		**2d**	1 h	54 (%) **4d**	88 (%)
3		**2f**	1 h	62 (%) **4f**	85 (%)
4		**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).

Table 3 Stereoselective vinylation of **1a** with vinyl chlorides/triflates and subsequent hydrolysis

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

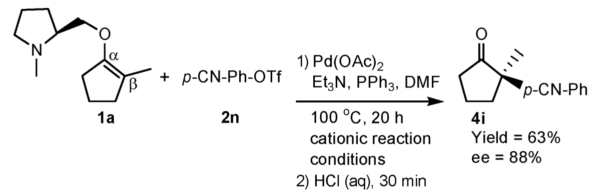
[a] The reactions were performed at 100 °C under air with **1a** (0.15 mmol) as the yield determining substrate using standard neutral conditions. Ketones were obtained after hydrolysis with concentrated HCl (aq). Isolated yields are average of three runs. Purity >95% by GC-MS. [b] Ee of (+) isomer of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

materials. To demonstrate the scope and applicability of this two-step, 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 Overman[15] and Shibasaki[4] 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 **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 conditions[16] 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 Et_3N (4.0 equiv), 6.0 mol% of $Pd(OAc)_2$ and 12.0 mol% of PPh_3 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 **2a–m** 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 iodides[12] and the only differences comprise the initial involvement of a T-shaped oxidative addition intermediate using the *t*-Bu$_3$P ligand,[17] instead of the tetra-substituted 16-electron square planar palladium complex produced with less bulky ligands. Recently published DFT calculations[18] 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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