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A palladium-catalyzed enantioselective reductive Heck reaction of enones using monodentate phosphoramidite ligands is described. α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL)-based phosphoramidites with palladium(II) acetate, and N-methyl dicyclohexylamine as reducing agent gives the reductive Heck product in high yields and enantioselectivities of up to 90%. The solvent plays an important role and in diethyl carbonate, the chemo- and enantioselectivity appeared to be the highest.

The transition-metal-catalyzed enantioselective conjugate addition of organometallics to activated alkenes is an attractive and widely applied method to create stereocenters.[1] A variety of organometallic reagents, for example, organoboron, -zinc, -aluminium, -silicon, -lithium, and -magnesium (Grignard) reagents have been used in combination with a plethora of Michael acceptors, and high levels of enantioselectivity have been achieved with a suitable chiral metal catalyst.[2] The enantioselective conjugate addition of hard organometallic compounds has been well explored in copper catalysis in particular,[3] whereas soft organometallics are mostly used in combination with rhodium[4] and palladium catalysts.[5] In sharp contrast, the direct use of the parent aryl or alkyl halides in enantioselective conjugate addition reactions is still underdeveloped although potentially more straightforward as it obviates the need for the preparation of the organometallic re-

agent. One reaction that can be used is the asymmetric Heck reaction, which, however, requires special substrates.[6]

The group of Cacchi[7] and our groups[8] extensively studied the palladium-catalyzed conjugate addition (also known as the reductive Heck reaction) of aryl iodides to enones and enals. In this process, the electrophilic halide acts as a nucleophile for which a stoichiometric reductant is needed. Until now, formates and trialkyl amines have been used successfully. Despite these developments, the asymmetric version of this reaction has been studied much less intensively, and an intermolecular version has not yet been reported. Nevertheless, a number of reports have appeared on the intramolecular version.[9] In 2007, Buchwald et al. reported the asymmetric reductive Heck reaction by using aryl triflates, nonaflates, and halides, using (R)-3,5-XylMeOBIPHEP as ligand.[9a] In most cases, moderate to good ee values were observed. In particular with aryl halides, the desired product was obtained in low yield and with moderate enantioselectivity. Jia and co-workers have developed an enantioselective arylative dearomatization of indoles using a reductive Heck reaction with BINAP as ligand.[9b] Recently, Zhou and co-workers studied the same reaction using aryl halides, especially bromide and chloride, and found that spiro-di(1,1′-indanyl)bisphosphine (SDP)-type ligands were superior, affording 3-arylindanones with high ee.[9c] The use of 1 equiv. of benzoic acid with 3 equiv. of trialkylamine in ethylene glycol was crucial to obtain high yields as wells as high enantioselectivities. Chiral 3-arylindanones are present in various natural products and are also used as intermediate to synthesize various bioactive molecules.[10] Other methods to prepare chiral 3-arylindanones through the cyclization of chalcone derivatives have also been reported.[11] Important examples include rhodium-catalyzed intramolecular asymmetric 1,4-addition of boryl substituted chalcones[12] and palladium-catalyzed Heck reaction of halogen substituted chalcones and their subsequent asymmetric reduction.[13] Since boryl substituted chalcones are prepared from the aryl halide precursor and the palladium-catalyzed cyclization reaction required two or more steps to obtain the desired product, it is advantageous to develop a novel method for the synthesis of chiral 3-arylindanones from easy accessible starting materials and a readily available chiral ligand in a single step fashion. Metal-catalyzed asymmetric cyclization reactions to prepare chiral 3-arylindanones[11] from different precursors, such as 2-alkenylbenzaldehyde,[14a,b] and 2-cyclobutanone substituted arylboronates,[14c] have also been described in the literature.

Monodentate phosphoramidite ligands form a readily available and easily tunable class of ligands that has proven

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successful in a variety of catalytic asymmetric transformations.[15] Their use as ligands in the Heck reaction has been reported as well,[16] including the successful use in an asymmetric Heck reaction (Scheme 1a).[17] Although many reports on the
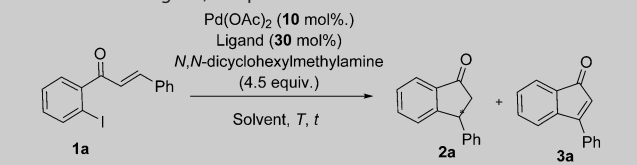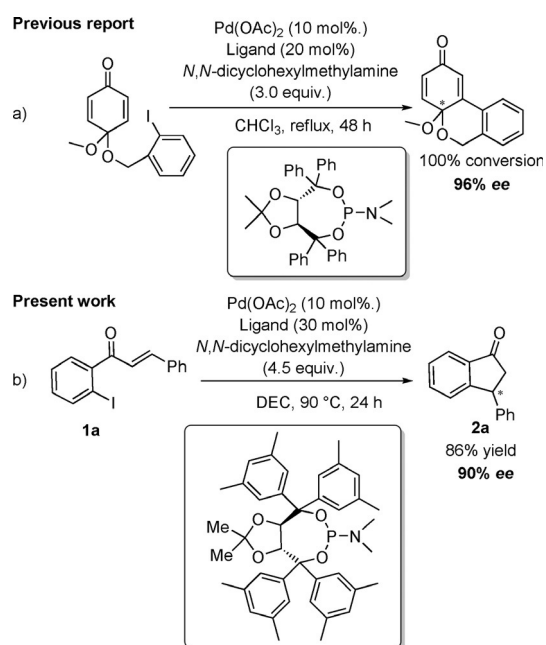

Scheme 1. Chiral phosphoramidite ligands applied in an asymmetric Heck[17] (a) and now in an asymmetric reductive Heck reaction (b).

use of chiral phosphoramidites as ligands in the transition metal-catalyzed asymmetric conjugate addition of organometallics have appeared, there is no report on their application in an asymmetric reductive Heck reaction.[15]

Herein, we report the palladium-catalyzed intramolecular asymmetric reductive Heck reaction of chalcones **1** using chiral monodentate phosphoramidite ligands.

Chalcone derivatives **1a**–**d** are easily prepared from the readily available starting materials 1-(2-iodophenyl)ethan-1-one and the corresponding benzaldehydes through aldol condensation.[9a] After synthesizing **1**, we studied the asymmetric reductive Heck reaction of **1a** in the presence of 10 mol% Pd(OAc)$_2$, ligand (30 mol%), and *N,N*-dicyclohexylmethylamine as reducing agent (4.5 equiv.). Our study commenced with a screening of chiral monodentate phosphoramidite ligands (Table 1). With the BINOL-based phosphoramidite **L1** in chloroform at 65 °C, the desired reductive Heck product **2a** was obtained in a satisfying 81 % yield but with a moderate 51 % *ee* (entry 1). In addition, the competitive Heck product **3a** was also formed in 11 % yield. To improve the enantioselectivity in the formation of **2a** and to suppress the formation of **3a**, the reaction was examined in a variety of solvents (entries 2–5). Despite the moderate conversion, 1,2-dimethoxy ethane (DME) seemed to be more suitable than other solvents in terms of both selective formation of **2a** and enantioselectivity (entry 4). Although 1,4-dioxane gave good conversion, the considerable amount of Heck product made it less effective (entry 5). The

Table 1. Palladium-catalyzed intramolecular asymmetric reductive Heck reaction of chalcone **1a** using monodentate phosphoramidite ligands. Variations in the ligand, temperature and the solvent.[a]

Entry	L	Solvent	T [°C]	t [h]	Conv. [%] 1a	Yield[b] [%] 2a	Yield[b] [%] 3a	ee [%] 2a
1	L1	CHCl$_3$	65	24	100	70	15	51
2	L1	THF	80	48	40	5	25	50
3	L1	DCE	80	24	45	8	30	30
4	L1	DME	80	24	55	50	5	66
5	L1	1,4-dioxane	80	48	81	52	26	60
6	L2	DME	80	24	46	40	3	40
7	L3	DME	80	6	100	86	6	11
8	L4	DME	80	52	100	88	5	74
9	L4	DME	65	72	40	35	3	91
10	L4	dimethyl carbonate	80	48	100	88	6	80
11	L4	diethyl carbonate	80	48	100	87	5	86
12	L5	diethyl carbonate	90	24	100	92 / 86[c]	6	90
13	L5	ethylene carbonate	80	18	82	60	10	91
14	L1	diethyl carbonate	80	24	58	51	4	73

[a] All reactions were performed using **1a** (0.22 mmol), catalyst (10 mol %), ligand (30 mol %), amine (1 mmol), in 2.0 mL of solvent and *n*-decane as internal standard for 6–72 h. [b] GC yields. [c] Isolated yield.
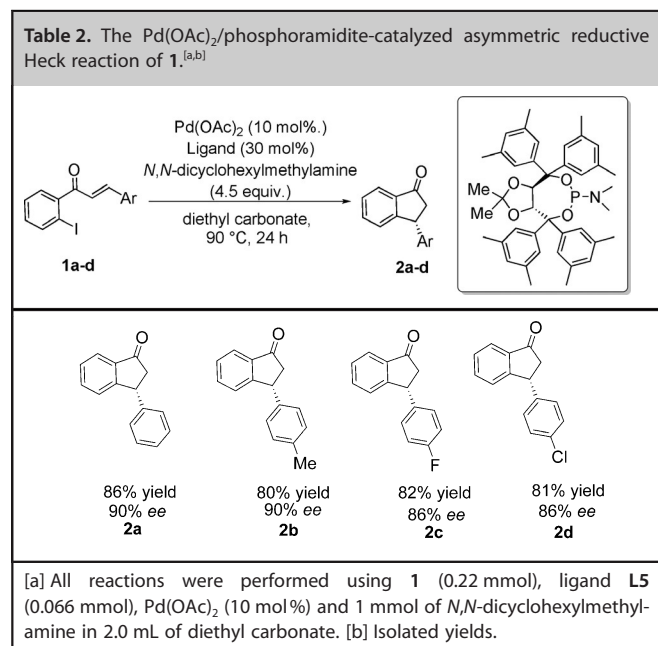
use of other solvents such as THF and 1,2-dichloroethane induced only moderate *ee* values.

In an attempt to identify a more selective ligand, we then screened the reaction with other chiral phosphoramidite ligands **L2**–**L4** using DME as the solvent (entries 6–8). No promising results were observed with **L2** and **L3**, however, if α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol-derived phosphoramidite **L4**[18] was used as ligand, the reaction proceeded smoothly to afford **2a** in 88 % yield with 74 % *ee*. Decreasing the temperature of the reaction led to an increase of the *ee* to 91 %, though at the expense of the yield which was only 35 % even after 72 h (entry 9). To improve the reaction rate and enantioselectivity, and keeping in mind the profound influence of the solvent, we also studied the effect of dialkyl

carbonate solvents, which have been advocated by the group of Börner for the use in asymmetric catalysis (entries 10–14).[19] With ligand **L4**, in combination with dimethyl carbonate as solvent, the reaction of **1a** proceeded well to give **2a** in 88% yield with 80% *ee*. Pleasingly, a higher enantioselectivity was observed with diethyl carbonate. Finally, changing the ligand to **L5** but keeping diethyl carbonate as the solvent improved the reaction rate and enantioselectivity, giving **2a** in 86% isolated yield with 90% *ee* in 24 h.

After having established the optimal reaction conditions, we studied the reaction with various chalcones (**1b–d**). As shown in Table 2, both electron-donating and -withdrawing

Table 2. The Pd(OAc)$_2$/phosphoramidite-catalyzed asymmetric reductive Heck reaction of **1**.[a,b]

86% yield 90% *ee* **2a**	80% yield 90% *ee* **2b**	82% yield 86% *ee* **2c**	81% yield 86% *ee* **2d**

[a] All reactions were performed using **1** (0.22 mmol), ligand **L5** (0.066 mmol), Pd(OAc)$_2$ (10 mol%) and 1 mmol of *N,N*-dicyclohexylmethylamine in 2.0 mL of diethyl carbonate. [b] Isolated yields.

substituents are allowed in the β-phenyl substituent, although a slight decrease in the enantioselectivity was observed for electron withdrawing substituents. For instance, **1b** gave the reductive Heck product in 80% yield with 90% *ee*, and the halide containing chalcones **1c** and **1d** gave the corresponding products **2c** and **2d** in good yield with 86% *ee*. We also examined the reaction with (*E*)-1-(2-bromophenyl)-3-phenylprop-2-en-1-one **1e**, in which the reductive Heck product **3e** was obtained in 55% yield with 82% *ee* (Scheme 2). The low yield is a result of the poor conversion of **1e** even after 3 days.
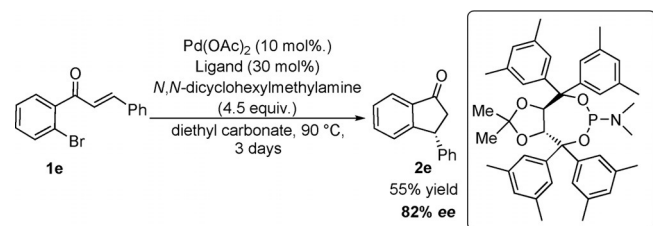
Scheme 2. Asymmetric reductive Heck reaction of (*E*)-1-(2-bromophenyl)-3-phenylprop-2-en-1-one (**1e**).

Compared to earlier studies on the asymmetric intramolecular reductive Heck (AIRH) reaction,[8] our present catalyst system is more effective in the enantioselective cyclization of (*E*)-2-iodo chalcones and functions to a lesser extent with (*E*)-2-bromo chalcones. In contrast to the method of Zhou et al.,[8c] we did not require an acid additive such as benzoic acid to obtain good yields and high enantioselectivities. Although Zhou's catalytic system works very well with aryl bromides, affording 3-arylindanones with high *ee*, examples involving aryl iodides were not described. Our catalyst system provides an excellent opportunity to use aryl iodides in the AIRH reaction.

In conclusion, an efficient palladium-catalyzed enantioselective reductive Heck reaction of chalcones, using TADDOL-based monodentate phosphoramidite ligands, has been developed. Good yields and high enantioselectivities up to 90% are reached for the first time in an asymmetric reductive Heck reaction with monodentate ligands. The enantioselectivities are higher than those observed by Buchwald and co-workers[9a] but slightly lower than those observed by Zhou and co-workers.[9c] However, the ligand used here is substantially cheaper than the bisphosphines they use. In addition, the present method does not require the addition of stoichiometric benzoic acid. Another advantage is the use of diethyl carbonate as solvent (b.p. 90 °C), which is much easier to remove than ethylene glycol (197 °C). The reasons for the beneficial properties of diethyl carbonate as solvent with respect to reaction rate and enantioselectivity are currently unclear. Carbonates have been found to be beneficial solvents for a range of transition metal catalyzed reactions.[19] It is possible to speculate that the relatively high polarity of the solvent paired with its low propensity to coordinate to the metal plays a role.

Extension of the scope of the reaction and the role of the solvent is currently under study.

Experimental Section

General procedure for the asymmetric reductive Heck (ARH) reaction of 1. In a flame dried Schlenk tube equipped with a septum and stirring bar, Pd(OAc)$_2$ (10 mol%, 0.022 mmol, 5.0 mg) and ligand **L6** (30 mol%, 0.066 mol, 43.5 mg) were dissolved in anhydrous diethyl carbonate (DEC, 1.0 mL) and stirred under nitrogen at room temperature for 5 min. Chalcone **1** (75 mg, dissolved in 1.0 mL of DEC; 0.224 mmol) was added, followed by the addition of *N,N*-dicyclohexylmethylamine (1 mmol), with constant stirring. Then, the Schlenk tube was placed into a preheated oil bath at 65 °C and stirred for 30 min. Finally, the reaction mixture was heated to 90 °C and stirred for 24 h. Upon completion (as judged by GC/MS), the reaction mixture was cooled down to room temperature, diluted with either diethyl ether or ethyl acetate, and filtered through a Celite and silica gel pad. The filtrate was concentrated and the residue was purified on silica gel chromatography to afford the desired product **2**.

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