Asymmetric Synthesis

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Highly Enantioselective Pd-Catalyzed Allylic Alkylations of Acyclic Ketones**

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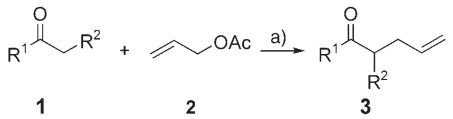
Since the first example of Pd-catalyzed asymmetric allylic alkylation (AAA) was reported by Trost and Strege,[1] great achievements in this area of chemistry have been made. Today, AAA is not only a well-studied transition-metal-catalyzed asymmetric reaction but also one of the most important asymmetric carbon–carbon bond-forming reactions.[2] As a diversity of bond types can be formed and many chiral elements can be installed at the nucleophile, the electrophile, or both, transition-metal-catalyzed AAAs have become a powerful tool in organic synthesis.[2c] Although a variety of substrates and reagents are suitable in AAA reactions, the use of carbon nucleophiles is mainly limited to the stabilized "soft" carbanions such as β-keto ester and malonate derivatives.[2] Simple ketone enolates are an important class of nucleophiles, but AAA had been ineffective with these nucleophiles because they are nonstabilized and hard. The breakthrough came in 1999, when Trost and Schroeder obtained high enantioselectivity in Pd-catalyzed AAAs with tetralone and cyclohexanone derivatives by using a "chiral pocket" ligand.[3] Since then, several examples were reported and excellent enantioselectivities were obtained.[4,5] Cyclic ketones have been used as substrates in these reactions. Recently, Braun et al. reported the Pd-catalyzed allylic alkylation of 1,3-diphenylallyl acetate with high diastereoselectivity by using mesityl ethyl ketone.[4c] However, the reaction was not asymmetric. Thus, an asymmetric version of Pd-catalyzed AAAs with acyclic ketones remains a challenge. Recently, we designed some ferrocene-derived chiral P,N ligands and employed them successfully in Pd-catalyzed AAAs.[5,6] High regio- and enantioselectivities were provided by using monosubstituted allyl derivatives as substrates and by using cyclic ketones as nucleophiles. For Pd-catalyzed AAAs with acyclic ketones to be enantioselective, we have modified the ligands. Herein, we report our preliminary results in the synthesis of a novel chiral ligand and its application to a Pd-catalyzed asymmetric allylic reaction that uses acyclic ketones as nucleophiles.

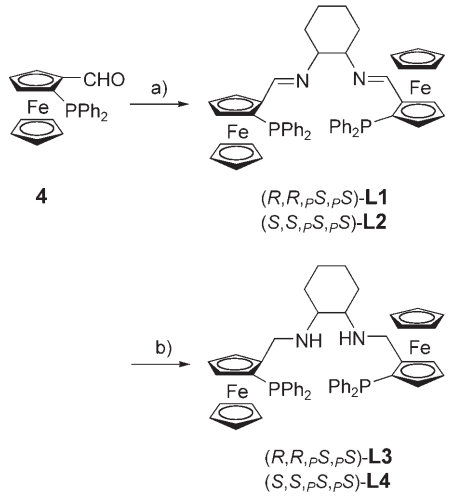
Initially, we examined the reaction of 1-phenyl-propan-1-one (**1a**) with allyl acetate (**2**) in the presence of [{Pd(C_3H_5)Cl}$_2$] and a variety of ligands,[6a] but we obtained no encouraging results (Scheme 1). All reactions gave almost no



Scheme 1. a) [{Pd(C_3H_5)Cl}$_2$] (2.5 mol%), ligand (5 mol%), lithium 1,1,3,3-hexamethyldisilazane (LiHMDS), THF, 0°C.

desired product **3a** under these conditions. According to the reports by Trost et al.[3,4a] as well as our own previous work,[5] chiral pocket ligands have emerged as ligands of choice for the highly enantioselective allylic alkylation of simple cyclic ketone enolates. Thus the modified chiral pocket imine and amine deriviatives **L1**–**L4**[8] were synthesized from ferrocene **4**[7] (Scheme 2).

In the presence of **L3**, the reaction of **1a** with **2** gave the allyl product **3a** in 69% yield and with 31% *ee*, whereas in the presence of **L4**, the reaction gave **3a** in 23% yield and with 2.5% *ee*. The lower yield and enantioselectivity is attributed to the mismatched chiralities in **L4**.[9] A further increase in the enantioselectivity (from 31% to 48% *ee*) was observed when **L1** was used in place of **L3**. The choice of base is important: the use of sodium hydride or potassium *tert*-butoxide in conjunction with ligand **L1** led to very low yields. The use of a



Scheme 2. Synthesis of ligands **L1**–**L4**. Reagents and conditions: a) (*S*,*S*)- or (*R*,*R*)-cyclohexane-1,2-diamine, *p*-TsOH, 4-Å MS, toluene; b) $NaBH_4$, EtOH.

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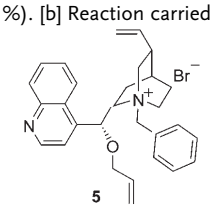
bulkier base such as LiHMDS led to a slight increase in both yield (77%) and enantioselectivity (57% *ee*), and the use of lithium tetramethylpiperidine gave the product in 48% yield with 56% *ee*. The metal ion of the base has a great effect on the yield and enantioselectivity of the reaction. For example, the reaction with LiHMDS gave the product in 77% yield and with 57% *ee*, but the corresponding reactions with NaHMDS and KHMDS provided products with 2% *ee* and 9% *ee*, respectively, although the yields were higher. A study of the effect of solvent on the reaction showed that among the solvents tested (Et_2O, 1,4-dioxane, 1,2-dimethoxyethane, toluene), THF gave the best results.

On the basis of these results, we envisioned that the lithium enolate derived from an α-alkoxy-substituted ketone would provide a general approach to the control of enantioselectivity in the AAA of acyclic ketones due to the propensity of this ketone to form the *Z*-chelated enolate. Our results demonstrate that the alkoxy group exhibits a remarkable effect on the level of enantioselectivity. When 1-phenyl-3-methoxypropan-1-one (**1b**) was used with LiHMDS as base, the enantioselectivitiy significantly increased to 68% *ee* and the yield was 72%. Takemoto and co-workers as well as Wang reported that chiral ammonium salts have a dramatic effect on the enantioselectivity of Pd-catalyzed AAA reactions.[10] In our case, the ammonium salts, both chiral and achiral, also showed an ability to improve the enantioselectivity of the reaction (see Table 1). We inferred that this

Table 1: The effect of additives on the reaction.[a]

Entry	Additives	Yield [%]	*ee* [%]
1	Bu_4NBr	48	75
2	Hex_4NBr	62	75
3	**5**	60	74
4	$ZnCl_2$	66	83
5	$CuClO_4$	70	89
6	AgOTf	84	87
7	Ag_2O	89	73
8	AgBr	96	89
9	AgBr	98[b]	93[b]

[a] Reactions performed at 0°C; $[\{Pd(C_3H_5)Cl\}_2]$ (2.5 mol%); **L1** (5.0 mol%); additives (10 mol%); LiHMDS (120 mol%); **1b** (100 mol%); **2** (130 mol%). [b] Reaction carried out at −20°C.



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increase in enantioselectivity in the presence of ammonium salts is caused to some extent by their Lewis acid character. Thus, several Lewis acids were tested (see Table 1).[11]

Lewis acids have a greater effect on the reaction than ammonium salts. Among the Lewis acids tested, silver bromide gave the best result both in terms of enantioselectivity and yield. When the reaction proceeded at −20°C in the presence of a catalytic amount of AgBr, the product was obtained in 98% yield with 93% *ee*. The effect of the amount of catalyst on the reaction was also studied. Reducing the catalyst amount to 1 mol% gave rise to a slight decrease in both yield (93%) and enantioselectivity (90% *ee*). When the amount of catalyst was decreased to 0.5 mol%, the reaction still proceeded smoothly to give the product in 83% yield with 90% *ee*. Under these optimized conditions, a variety of acyclic ketones were tested (see Scheme 1) and the results are given in Table 2.

Table 2: Pd-catalyzed AAA of acyclic ketones **1**.[a]

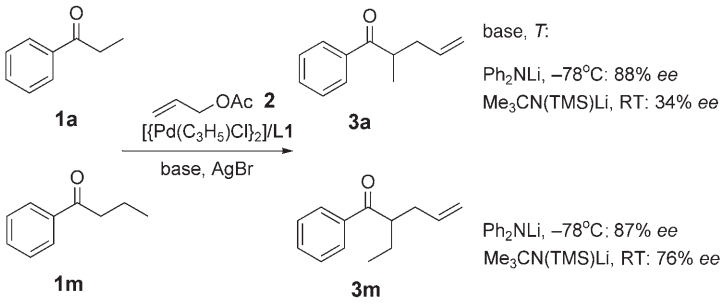
		Substrate **1**		Product **3**	
Entry		R^1	R^2	Yield [%][b]	*ee* [%][c]
1	**a**	Ph	Me	93	77
2	**b**	Ph	OMe	98	93
3	**c**	Ph	OEt	88	92
4	**d**	Ph	O*i*Pr	95	79
5	**e**	*p*-$MeOC_6H_4$	OMe	83	94
6	**f**	*p*-ClC_6H_4	OMe	91	91
7	**g**	Ph	Ph	89	73
8	**h**	*c*Hex	OMe	76	87
9	**i**	2-furyl	Me	50	80
10	**j**	Ph	OAc	50	86
11	**k**	Ph	OPh	89	71
12	**l**	Ph	SO_2Ph	83	0

[a] All reactions were performed at −20°C; $[\{Pd(C_3H_5)Cl\}_2]$ (2 mol%); **L1** (4 mol%); **1** (100 mol%); LiHMDS (120 mol%); **2** (130 mol%); AgBr (10 mol%). [b] Yield of isolated product. [c] Determined by chiral HPLC.

All acyclic nonstabilized hard ketones gave products in good to excellent yields and enantioselectivities. However, the stabilized soft ketone **1l** gave a racemic product (entry 12, Table 2). The nature of the alkoxy substituent has a great effect on the enantioselectivity. Substrates **1b** and **1c** with less sterically hindered MeO and EtO groups gave the corresponding allylated products with *ee* values of 93% and 92%, respectively (entries 2 and 3, Table 2). However, the substrates with the bulky *i*PrO, **1d**, and PhO, **1k**, furnished products with *ee* values of 79% and 71%, respectively, although the yields were good to excellent (entries 4 and 11, Table 2). It was unexpected that the reactivity of ketone **1j** with the ester substituent would be so low, although the enantioselectivity was good (50% yield and 86% *ee*; entry 10, Table 2). The electronic property of the substituent on the phenyl ring of the substrate has little effect on the reaction. Thus, the methoxy-substituted aryl ketone **1e** and the chloro-substituted aryl ketone **1f** gave allylated products with 94% and 91% *ee*, respectively. Importantly, the aliphatic cyclohexyl methoxymethyl ketone (**1h**) afforded the corresponding product in 76% yield with 87% *ee* (entry 8, Table 2). The heteroaryl-substituted simple ketone **1i** gave rise to the corresponding product in 50% yield with 80% *ee*.

Under different conditions, *Z* or *E* forms of an enolate are favored,[12] which may influence the enantioselectivity of the alkylation. Xie et al. reported that the *Z* form of an enolate was formed exclusively by using Ph_2NLi at −78°C, while *Z* and *E* forms of an enolate were provided in a ratio of 48:52 with $Me_3CN(TMS)Li$ (TMS = trimethylsilyl) as base at room temperature.[12] In the reactions reported here, we found that different forms of an enolate dramatically affected the

enantioselectivity of a reaction. In the presence of Ph_2NLi at −78 °C, the reaction of ketone **1a** gave the product **3a** with 88% *ee*. Even phenyl propyl ketone (**1m**) gave the product **3m** with 87% *ee*, but only enantioselectivities of 34% and 76% *ee* were obtained with $Me_3CN(TMS)Li$ (Scheme 3).



Scheme 3. The reactions of **1a** and **1m** to form **3a** and **3m**, respectively.

These results may explain why substrates with an alkoxy group at the α-position of the carbonyl group led to products with high enantioselectivities. The presence of AgBr did not influence the ratio of *Z* and *E* isomers of an enolate: the reaction of **1a** with **2** in the presence of NaHMDS and AgBr gave **3a** with 9% *ee*.

In conclusion, we have synthesized a novel chiral imino ferrocene ligand and used this ligand to carry out highly enantioselective Pd-catalyzed allylic alkylations of simple acyclic ketones. The dramatic effect of AgBr as well as the dependency of the enantioselectivity on the different forms of the enolate have been demonstrated. Further investigations on the role of AgBr and the applications of the ligand **L1** in other types of acyclic ketones are in progress.

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