Asymmetric Catalysis

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Highly Enantioselective Palladium-Catalyzed Alkylation of Acyclic Amides**

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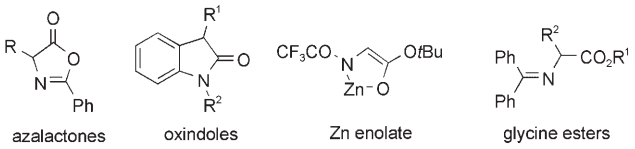
Dedicated to Professor Emanuel Vogel on the occasion of his 80th birthday

Transition-metal-catalyzed asymmetric allylic alkylation (AAA) has found wide application in organic synthesis as a powerful tool for the enantioselective formation of carbon–carbon and carbon–heteroatom bonds.[1] A variety of nucleophiles have been used in this reaction, in which stereogenic centers can be produced in either the allylic substrate, the nucleophile, or both. However, for a long time, carbon nucleophiles were limited to "soft" or stabilized carbanions. A breakthrough was made in 1999 by Trost and Schroeder, who reported a highly enantioselective alkylation with enolates derived from cyclic ketones.[2] Since then, enolates derived from simple ketones and aldehydes have been applied successfully in the AAA reaction.[3–5]

Carboxylic acid derivatives are an extremely useful class of compounds in organic synthesis. However, it is more difficult to use carboxylic acid derivatives in AAA reactions because of the lower acidity of their α hydrogen atom and the even less stabilized nature of carbanions derived from such compounds. To date, no report on the use of carboxylic acid derivatives in transition-metal-catalyzed AAA reactions has appeared, although the use of a few special carboxylic acid derivatives with additional carbanion-stabilizing features, such as azalactones, [6] 3-substituted oxindoles,[7] glycine esters, [8a,d,9] and Zn enolates of glycine and peptides,[8b,c,e] has been reported (Scheme 1).[10] Transition-metal-catalyzed AAA with carbon nucleophiles derived from general carboxylic acid derivatives remains a great challenge. Previously, we developed a series of 1,1′-P,N ferrocene ligands and applied them in Pd-catalyzed regio- and enantioselective allylic alkylation reactions.[5,11] Recently, we also demonstrated, as did Trost and Xu, that acyclic ketone enolates are suitable nucleophiles for Pd-catalyzed AAA reactions.[3h,5d,e] To extend the scope of "hard" nonstabilized carbanions as nucleophiles in transition-metal-catalyzed AAA reactions, we turned our attention to carboxylic acid derivatives. Herein we report that α-carbanions of acyclic amides are suitable nucleophiles for Pd-catalyzed AAA: We observed high enantioselectivity with 1,1′-P,N ferrocene compounds as ligands.



Scheme 1. The structures of some special carboxylic acid derivatives used in transition-metal-catalyzed AAA reactions.

When we treated phenyl propionate with allyl acetate (**2a**) in the presence of the ligand (S,R_{phos},R)-**L1** (5 mol%) and [{Pd(C_3H_5)Cl}$_2$] (2.5 mol%), we observed no product formation. We next investigated the use of amides **1** as substrates in the hope that the substituents on the amide nitrogen atom might affect the reactivity of the substrate.[12] Indeed, the nature of the substituents on the nitrogen atom of the amide has a critical effect on the reaction (Table 1).[13]

Whereas none of the desired product was observed when the *N*,*N*-dimethyl, *N*-phenyl, *N*-methyl-*N*-phenyl, and *N*-Boc-*N*-methyl amides **1a–d** were used (Table 1, entries 1–4), a trace amount of the product was observed with the *N*-pyrrol-1-yl amide **1e** (Table 1, entry 5). When the amide **1f** with phenyl and Boc groups on the nitrogen atom was used, the product was obtained in about 20% yield (Table 1, entry 6). The yield increased to about 40% when **1g**, with two phenyl groups on the nitrogen atom, was used (Table 1, entry 7). Although two methyl substituents are present on the nitrogen atom of the amide **1p**, the desired allylated product was obtained in 65% yield upon treatment with **3a**, probably because the phenyl ring stabilizes the carbanion produced from **1p** (Table 1, entry 8).[13] However, only low enantiose-

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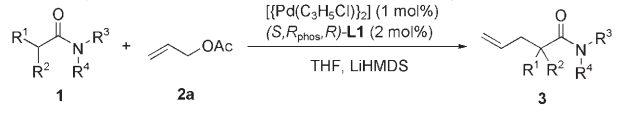
Table 1: Optimization of the amide **1** in the Pd-catalyzed AAA reaction.[a]



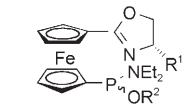
1 **2a** **3**

Entry	Amide **1** R^1, R^2	R^3, R^4	**1**, **3**	Lig.	Yield [%][b]	*ee* [%][c]
1	Me, H	Me, Me	**a**	**L1**	NR	–
2	Me, H	H, Ph	**b**	**L1**	NR	–
3	Me, H	Me, Ph	**c**	**L1**	NR	–
4	Me, H	Me, Boc	**d**	**L1**	NR	–
5	Me, H	-CH=CH-CH=CH-	**e**	**L1**	trace	–
6	Me, H	Ph, Boc	**f**	**L1**	20	–
7	Me, H	Ph, Ph	**g**	**L1**	40	47 (+)
8	Ph, H	Me, Me	**p**	**L1**	65	45 (+)
9	Me, H	Ph, Ph	**g**	**L2**	60	28 (+)
10	Me, H	Ph, Ph	**g**	**L3**	54	46 (+)
11	Me, H	Ph, Ph	**g**	**L4**	70	50 (+)
12	Me, H	Ph, Ph	**g**	**L5**	60	29 (−)
13	Me, H	Ph, Ph	**g**	**L6**	71	60 (−)
14	Me, H	Ph, Ph	**g**	**L7**	35	31 (+)
15	Me, H	Ph, Ph	**g**	**L8**	65	55 (+)
16	Me, H	Ph, Ph	**g**	**L9**	70	0

[a] Molar ratio: **1**/[{Pd(C_3H_5)Cl}$_2$]/ligand/LiHMDS/**2** 100:1:2:100:200. [b] Yield of **3** after isolation by preparative TLC. [c] The *ee* value of **3** was determined by HPLC on a chiral phase. The sign of optical rotation is given in brackets. Boc = *tert*-butoxycarbonyl, HMDS = hexamethyldisilazide, NR = no reaction.

lectivity was observed in the reactions of **1g** and **1p** (Table 1, entries 7 and 8).

Next, we screened ligands with different substituents on the oxazoline ring and with different chiral elements (Scheme 2) in the reaction with the substrate **1g**. We observed



L1-L4 and **L7-L9**:
R^2 = (*R*)-1,1'-bi-2-naphthol
L5-L6:
R^2 = (*S*)-1,1'-bi-2-naphthol

R^1 = *i*Pr	(S,R_{phos},R)-**L1**
R^1 = *t*Bu	(S,R_{phos},R)-**L2**
R^1 = Ph	(S,R_{phos},R)-**L3**
R^1 = Bn	(S,R_{phos},R)-**L4**
R^1 = *i*Pr	(S,R_{phos},S)-**L5**
R^1 = *i*Pr	(S,S_{phos},S)-**L6**
R^1 = *i*Pr	(S,S_{phos},R)-**L7**
R^1 = H	(S_{phos},R)-**L8**
R^1 = H	(R_{phos},R)-**L9**

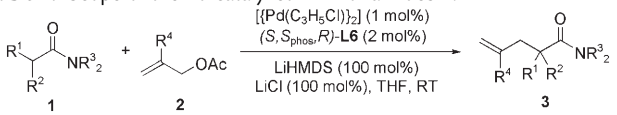
Scheme 2. Ferrocene-based P,N ligands.

the best results with (S,S_{phos},S)-**L6**, which has an isopropyl substituent on the oxazoline ring: The corresponding product was formed in 71% yield with 60% *ee* (Table 1, entry 13). The use of ligands with Ph, Bn, *t*Bu, and *i*Pr as the substituent led to the product in slightly lower yield with lower enantioselectivity (Table 1, entries 9–12). The product **3g** was also obtained in 65% yield and with 55% *ee* when the ligand **L8** with no stereogenic center in the oxazoline ring was used (Table 1, entry 15). However, with **L9**, the diastereoisomer of **L8**, **3g** was obtained in 70% yield with 0% *ee* (Table 1, entry 16). Clearly the chiral elements in **L9** are mismatched in this reaction. The configuration of the product (see below) is determined by the configuration of the binol component of the catalyst rather than that of the P atom (Table 1, entries 7–11, 14, and 15 versus entries 12 and 13), in contrast to our previous results.[5b,c,11]

We investigated the influence of the reaction conditions on the outcome of the reaction. THF was found to give better results than several other common solvents tested. The reaction gave the desired amide only when bases with lithium as the counterion, such as LiHMDS, lithium diisopropylamide, and *s*BuLi, were used. No product was observed when NaHMDS, KHMDS, *t*BuOK, or NaH were used. The yield and *ee* value of the product increased to 82 and 85%, respectively, if 1 equivalent of LiCl was used as an additive in the reaction with **L6** as the ligand and the amide substrate **1g**.[14,15] On the other hand, both the yield and the enantioselectivity decreased if HMPA (10 mol%; hexamethylphosphoramide) was added. These results also demonstrate the importance of lithium ions in the reaction. The amount of base used is also important. The presence of excess base led to a decrease in the *ee* value of the product because of racemization of the product.[16] The temperature was found to influence the reaction time and the yield of the product, but not the enantioselectivity of the reaction. Furthermore, the product was formed in higher yield with a higher *ee* value when allyl acetate was used instead of allyl carbonate or allyl phosphonate.

We studied the scope of the reaction with respect to the amide **1** under the optimized reaction conditions (Table 2). Quite a broad range of amides were transformed into the corresponding allylic products **3** in good to excellent yields and with high enantioselectivity. The R^1 group can be a primary or a secondary alkyl group (Table 2, entries 1–4 and 11), a phenyl group (entries 5, 9, 10, and 12), or a heteroatom functional group (entries 6–8). The R^2 group can be H (Table 2, entries 1–7 and 10–12) or Me; in the latter case, a stereogenic quaternary center was installed (Table 2, entries 8 and 9). 2-Methylallyl acetate is also a suitable allylation reagent, with the corresponding products formed in high

Table 2: Scope of the Pd-catalyzed AAA of amides **1**.[a]



1 **2** **3**

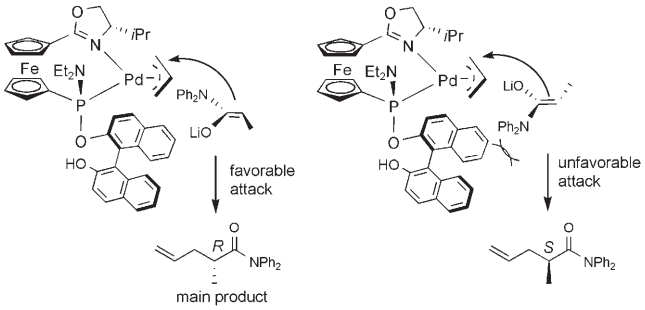
Entry	R^1	R^2	R^3	R^4	**3**	Yield [%][b]	*ee* [%][c]
1	Me	H	Ph	H	**g**	82	85
2	Et	H	Ph	H	**h**	78	82
3	Pr	H	Ph	H	**i**	75	83
4	*i*Pr	H	Ph	H	**j**	80	73
5	Ph	H	Ph	H	**k**	98	88
6	*N*-piperidinyl	H	Ph	H	**l**	95	86
7	TBSO	H	Ph	H	**m**	78	91
8	PhO	Me	Ph	H	**n**	99	93
9	Ph	Me	Ph	H	**o**	75	93
10	Ph	H	Me	H	**p**	75	88
11	Me	H	Ph	Me	**q**	85	91
12	Ph	H	Ph	Me	**r**	90	91

[a] Molar ratio: **1**/[{Pd(C_3H_5)Cl}$_2$]/(S,S_{phos},S)-**L6**/LiHMDS/**2**/LiCl 100:1:2:100:200:100. [b] Yield of **3** after isolation by preparative TLC. [c] The *ee* value of **3** was determined by HPLC on a chiral phase.

yields with high enantioselectivity (Table 2, entries 11 and 12).

The absolute configuration of the allylation products **3g** and **3h** was determined to be *R* by comparison of their HPLC trace (chiral phase) and the sign of their optical rotation with those of the synthetic samples (*R*)-2-methyl-*N*,*N*-diphenylpent-4-enamide (**3g**) and (*R*)-2-ethyl-*N*,*N*-diphenylpent-4-enamide (**3h**). These samples of known configuration were prepared by the resolution of 2-methylpent-4-enoic acid and 2-ethylpent-4-enoic acid, respectively, by using a chiral quinine, followed by successive treatment with oxalyl chloride and diphenylamine according to literature procedures.[17]

We propose a plausible model, in which the binol subunit and Nu^- (the α-carbanion of the amide) are on the same side of (below) the π-allyl moiety, to explain the observed stereochemical course of the reaction (Scheme 3):[18] *Re* attack to provide the *R* product is favored.



Scheme 3. Plausible transition state for the Pd-catalyzed AAA of allyl acetate with an amide.

In summary, high enantioselectivity was observed in the Pd-catalyzed AAA of acyclic amides in the presence of 1,1′-P,N ferrocene ligands to provide the corresponding γ,δ-unsaturated amides, which are useful building blocks in organic synthesis.[19] The nature of the substituents on the nitrogen atom of the amides has a great impact on the efficiency and selectivity of the reaction. Further studies are in progress towards the extension of the scope of the reaction and the application of this methodology in organic synthesis. We are also investigating the unusual stereochemical aspects of the reaction.

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[13] Density functional calculations at the B3LYP/6-31+G* level revealed that the reactivity of amides **1** depends on the stability

of the derived carbanion as follows: $\mathbf{1h}^- > \mathbf{1g}^- \sim \mathbf{1c}^- > \mathbf{1d}^- > \mathbf{1a}^-$.

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[15] Some other additives were also tested. The addition of Bu_4NCl or $Zn(OTf)_2$ (Tf = trifluoromethanesulfonyl) led to the formation of the product with better enantioselectivity than in the reaction with no additive, whereas the product was formed with lower enantioselectivity in the presence of CuI, CuCl, CuBr, $CuBr_2$, $Cu(OTf)_2$, AgBr, AgOTf, or $LiClO_4$, and none of the desired product was formed when LiBr, LiO*t*Bu, Bu_4NBr, or AcONa was added.

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