Asymmetric Catalysis

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Regioselective Catalytic Asymmetric C-Alkylation of Isoxazolinones by a Base-Free Palladacycle-Catalyzed Direct 1,4-Addition

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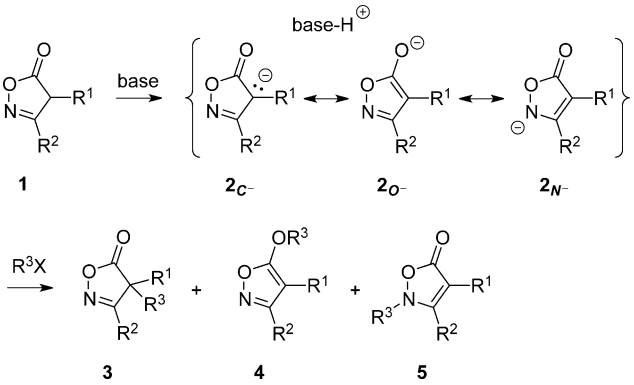
Abstract: *Isoxazolinones constitute a class of heterocycles utilized for the development of novel drug candidates. The cyclic oxime ester motif is also synthetically useful as it contains functional handles which have previously been used to provide access to an assortment of valuable compound classes not easily accessible by alternative approaches. However, asymmetric methods towards isoxazolinones are notoriously scarce. Herein we report the first catalytic asymmetric alkylations of isoxazolinones forming all-C-substituted quaternary stereocenters. The present studies were driven by the question of how to control the regioselectivity in the competition of different nucleophilic positions. The investigation of a direct 1,4-addition uncovered that a sterically demanding palladacycle catalyst directs the reactivity in the absence of a base nearly exclusively to the nucleophilic C atom, while at the same time it allows for high enantioselectivity and TONs up to 1900.*



Scheme 1. Reported regioselectivity problems in the alkylation of isoxazolinones **1**.[7]

Cyclic five-membered oxime esters, also called isoxazolinones (systematic name: 4*H*-isoxazol-5-ones), are broadly studied owing to their attractive pharmacological properties.[1] Isoxazolinones **1** are also interesting as valuable building blocks which permit, for example, a rapid access to β-amino acids[2] and to various classes of heterocyclic compounds. For instance, they have recently been described as a practical source for the generation of reactive vinylnitrene intermediates via oxidative addition of the reactive N–O bond to palladium(0) in order to provide bicyclic aziridines or highly substituted pyrroles.[3–5]

Despite the value of isoxazolinones for pharmaceutical sciences and organic synthesis, only little is known about the enantioselective preparation of chiral derivatives by asymmetric catalysis.[6] In particular, the generation of all-carbon-substituted stereogenic centers on the ring system by means of asymmetric catalysis has not yet been accomplished. One reason seems to be that alkylations of isoxazolinones **1** via the corresponding enolates **2** (Scheme 1) suffer from low regioselectivities due to the competition of nucleophilic C, N, and O centers, which are prone to alkylation with electrophiles.[7]

Herein, we report a catalytic asymmetric synthesis of isoxazolinones **3** that is capable of efficiently generating all-carbon-substituted quaternary stereocenters[8] on the heterocycle. A direct 1,4-addition,[9] which is catalyzed by a planar chiral palladacycle, proceeds with high regio- and enantioselectivity under neutral conditions and remarkably low catalyst loadings.

To address the regio- and enantioselectivity issue for this challenging class of substrates, the addition of isoxazolinone **1a** to methylvinylketone (**2A**, MVK) was investigated as a model reaction (Table 1).[10] Since we recently found that the ferrocene bisimidazoline bispalladacycle **[FBIP-Cl]$_2$**[11,12] is an efficient and practical precatalyst for asymmetric 1,4-additions of α-cyanoacetates[13] and azlactones,[14] we initially focused on this catalyst system.[15,16] In the absence of a catalyst, reactivity was low and only the N-alkylation product was detected (entry 1). Since a catalyst loading of 2.5 mol% **[FBIP-Cl]$_2$** provided only small amounts of 1,4-addition product **3aA** (entry 2), we utilized the reported catalyst activation procedure and added silver salts to remove the otherwise relatively inert chloride ligands.[11b] Activation by AgOTf resulted in a smooth conversion at room temperature in CH_2Cl_2. However, the activated catalyst triggered mainly the N-alkylation and the minor C-alkylation product was formed in nearly racemic form (entry 3). In contrast, using anionic ligands with an increased Lewis basicity like tosylate (entry 4) and heptafluorobutyrate (entry 5) resulted in a preference for the C-alkylation product, but the enantioselectivity remained moderate. Interestingly, the absolute configuration of the major enantiomer depended on the choice of the anionic ligand with carboxylates favoring the (*R*)-antipode (*ent*)-**3aA**.

The same observation was made with the mono-Pd precatalyst **[FIP-Cl]$_2$** activated by different silver salts (Table 1, entries 6 and 7).[17] In these cases good regioselectivity strongly favoring the C-alkylation product was found, but the product was still formed with only moderate

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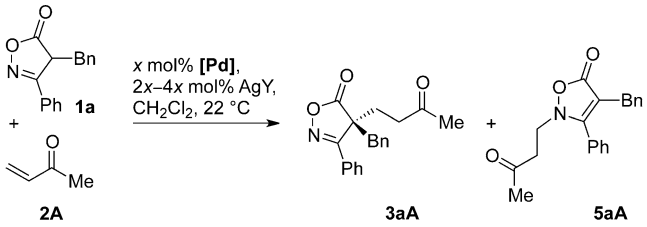
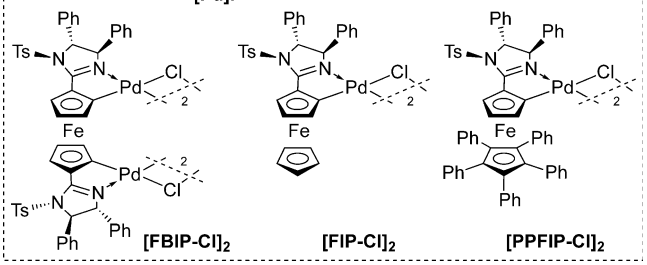
Table 1: Optimization of the model reaction.



[Pd]:



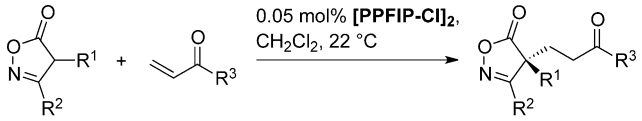
No.	[Pd]	x mol%	Y	Yield 3aA [%][a]	Yield 5aA [%][a]	ee 3aA [%][b]
1	–	–	–	0	5	–
2	**[FBIP-Cl]$_2$**	2.5	–	20	6	13
3	**[FBIP-Cl]$_2$**	2.5	OTf	29	71	10
4	**[FBIP-Cl]$_2$**	2.5	OTs	70	26	37
5	**[FBIP-Cl]$_2$**	2.5	O_2CCF_3	92	8	−27
6	**[FIP-Cl]$_2$**	2.5	OTs	94	6	43
7	**[FIP-Cl]$_2$**	2.5	O_2CCF_3	98	2	−34
8	**[PPFIP-Cl]$_2$**	2.5	OTs	93	7	78
9	**[PPFIP-Cl]$_2$**	2.5	O_2CCF_3	96	4	80
10	**[PPFIP-Cl]$_2$**	2.5	OAc	95	5	85
11	**[PPFIP-Cl]$_2$**	2.5	ClO_4	93	6	85
12	**[PPFIP-Cl]$_2$**	0.05	ClO_4	95	5	95
13	**[PPFIP-Cl]$_2$**	0.05	–	93	7	97

[a] Yield determined by ^{1}H NMR analysis using an internal standard. [b] Enantiomeric excess determined by HPLC. A minus sign indicates that the (*R*)-enantiomer was formed in excess.

enantioselectivity. With a sterically more demanding pentaphenylferrocene core as in **[PPFIP-Cl]$_2$**[17,18] it was possible to significantly improve the enantioselectivity (entry 8). Various silver salts were again screened for the catalyst activation using **[PPFIP-Cl]$_2$** (entries 8–11).[17,18] It was found that with this precatalyst always the (*S*)-enantiomer was formed in large excess no matter which silver salt was used. As the conjugate additions usually proceeded with full conversion in less than 1 h with 2.5 mol% of the precatalyst, much lower catalyst loadings were investigated and it was found that a loading of as little as 0.05 mol% still led to very high yields of the C-alkylation products and even enhanced enantioselectivity (entry 12). Surprisingly, also with the non-activated catalyst a loading of 0.05 mol% was found to be efficient in this case (entry 13). This is in contrast to the large majority of other reactions we have previously reported using this catalyst type and which require chloride exchange for a suitable reactivity to facilitate substrate coordination.[17–19]

The optimized reaction conditions were then applied to different substrates (Table 2). A range of isoxazolinones **1a–f** bearing a benzylic residue R^1 with different electron-withdrawing and -donating substituents in *meta* or *para* position

Table 2: Investigation of the reaction scope.



No.	3	R^1	R^2	R^3	Yield [%][a]	ee [%][b]
1	**3aA**	Bn	Ph	Me	93	96
2	**3bA**	$CH_2C_6H_4$-4-Me	Ph	Me	93	96
3	**3cA**	$CH_2C_6H_4$-4-OMe	Ph	Me	94	93
4	**3dA**	$CH_2C_6H_4$-4-NO_2	Ph	Me	79	96
5	**3eA**	$CH_2C_6H_4$-3-NO_2	Ph	Me	71	86
6	**3fA**	CH_2-2-naphthyl	Ph	Me	89	98
7	**3gA**	Ph	Ph	Me	77[c]	87
8	**3hA**	Me	Ph	Me	89	79
9	**3iA**	*n*-Pr	Ph	Me	95	85
10	**3jA**	Bn	4-O_2N-C_6H_4	Me	86	94
11	**3kA**	Bn	4-MeO-C_6H_4	Me	83	80
12	**3lA**	Bn	3-MeO-C_6H_4	Me	86	96
13	**3mA**	Bn	Me	Me	92[f]	68
14	**3oD**	$(CH_2)_4$		4-MeO-C_6H_4	88[g]	93
15	**3aB**	Bn	Ph	Et	92[d]	90
16	**3aC**	Bn	Ph	Ph	92[e]	91
17	**3aD**	Bn	Ph	4-MeO-C_6H_4	96[f]	97
18	**3aE**	Bn	Ph	$(CH_2)_2$Ph	94[f]	96

[a] Yield of isolated product **3** (0.5 mmol scale). [b] Enantiomeric excess of the isolated product determined by HPLC. [c] 0.15 mol% of **[PPFIP-Cl]$_2$** was used. [d] 0.2 mol% of **[PPFIP-Cl]$_2$** was used. [e] 0.5 mol% of **[PPFIP-Cl]$_2$** was used. [f] 1.0 mol% of **[PPFIP-Cl]$_2$** was used.

gave pleasing results in terms of reactivity (yield: 71–94%) and enantioselectivity (*ee* = 86–98%) using 0.05 mol% of **[PPFIP-Cl]$_2$** at 22 °C (entries 1–6). An aromatic residue R^1 directly connected to the 4-position of the isoxazolinone was also accommodated under the reaction conditions (entry 7), but also alkyl groups such as methyl and *n*-propyl allowed for high reactivity and useful enantioselectivity with low catalyst loadings (entries 8 and 9). The residue R^2 at the 3-position of the isoxazolinones could be modified, too. With π-acceptors (entry 10), π-donors (entry 11), and σ-acceptors (entry 12) on the aromatic moiety the reaction efficiency was always high. The *p*-OMe substituent led to a somewhat reduced enantioselectivity. Also alkyl residues directly connected to the 3-position of the isoxazolinones can be employed. While a substrate with the small methyl group provided the C-alkylation product **3mA** with only moderate enantioselectivity (entry 13), the bicyclic product **3oD** was formed in high yield and with an *ee* of 93% (entry 14). Both alkyl and aryl groups were also well tolerated as residues R^3 of the vinylketone substrates (entries 15–18).

The product constitution and absolute configuration were determined for compounds **3ma** and **3gA** by X-ray single-crystal structure analysis (see the Supporting Information).[20] The preferred (*S*)-configuration is in agreement with the mechanistic proposal shown in Figure 1. We suggest that the N center of the racemic isoxazolinone **1** coordinates to the azaphilic catalyst. In C,N-palladacycle complexes neutral substrates usually strongly prefer to adopt the position *trans* to the N donor.[11,12,18] By this coordination of the pronucleo-

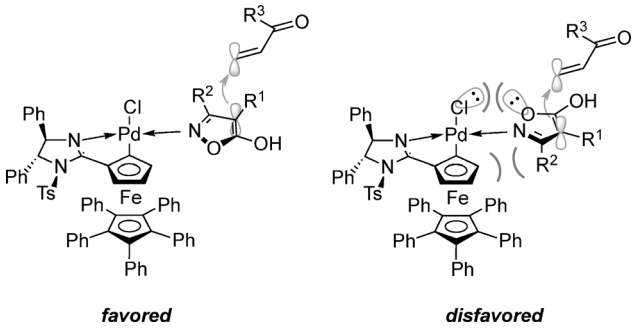
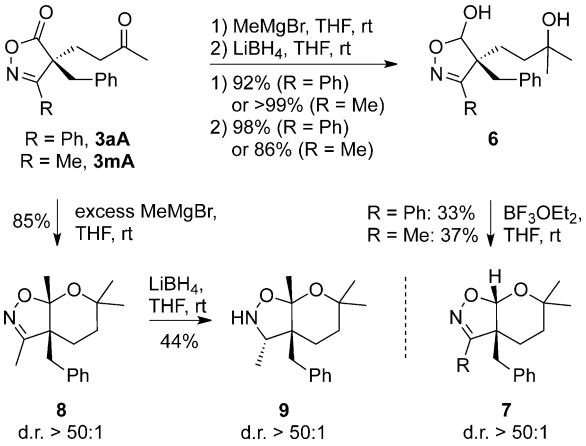


Figure 1. Mechanistic model to explain the stereochemical outcome of the 1,4-addition. Left: Favored reactive conformation; right: conformation that is disfavored due to steric and electrostatic repulsion.

philic substrate enolization is triggered. We suggest that the plane of the achiral heteroaromatic enol should be almost coplanar to the square-planar coordination sphere of the Pd^{II} center to minimize repulsion with the sterically demanding $Ph_5C_5^-$ spectator ligand. Two limiting conformations would be possible which are both depicted in Figure 1. The one depicted on the left is in agreement with the observed absolute configuration. We propose that this is the reactive conformation, because in the other conformation shown on the right there are repulsive steric interactions between R^2 and the ferrocene core as well as repulsive electrostatic interactions between a nonbonding orbital of the O(1) atom and the anionic chloride ligand. Attack of the vinylketone should occur from the *exo* direction, since the *endo* direction is shielded by the pentaphenylferrocene skeleton. This working model can explain 1) the positive effect of the $Ph_5C_5^-$ spectator ligand, 2) decreasing *ee* values with a smaller residue R^2 like methyl (Table 2, entry 13), and 3) lower *ee* values with larger anionic Pd ligands like tosylate (Table 1, entry 9).

As the products are densely functionalized, further synthetic manipulations can be envisaged and have already been described for the racemic 1,4-addition products **3**, including the synthesis of β-amino acids.[2–4,21] To confirm the synthetic value of the scalemic products **3**, we have repeated one of the reported sequences for the enantiomerically enriched compounds **3aA** and **3mA** to form bicyclic acetals **7** (Scheme 2).[2] Compounds with the tetrahydro-4*H*-pyrano[3,2-*d*]isoxazole skeleton are of interest for the development of new herbicides[22] and may display antibacterial and antiprotozoal activity,[23] but have (to our knowledge) not been available so far in enantioenriched form. Compound **7** could be formed in three steps in close analogy to the reported protocol[2] starting with a regioselective Grignard addition to the ketone function followed by a regioselective reduction of the isoxazolinone carbonyl group using $LiBH_4$. Cyclization with $BF_3{\cdot}OEt_2$ furnished the targeted structures in moderate yields as a single diastereomer. In addition, we found that treatment of **3mA** with an excess of Grignard reagent directly generated the bicyclic acetal **8** featuring two adjacent quaternary stereocenters in a single step with high yield and diastereoselectivity. Reduction of the C=N bond was achieved by $LiBH_4$ to provide isoxazolidine **9** featuring three adjacent stereocenters.[24]



Scheme 2. Synthesis of enantiomerically enriched tetrahydro- and hexahydro-4*H*-pyrano[3,2-*d*]isoxazoles.

In conclusion, the present report puts forward the first examples of enantioselective C-alkylations of isoxazolinones to form all-carbon-substituted quaternary stereocenters. The issue of regioselectivity could be addressed by the use of planar chiral monopalladacycle catalysts. High enantioselectivity was attained by the use of a sterically demanding pentaphenylferrocene backbone. The readily accessible racemic heterocyclic substrates are expected to undergo an enolization triggered by the palladacycle in the absence of any additional reagent. These mild conditions and very low catalyst loadings attenuate unwanted side reactions and allow for high atom economy in a direct 1,4-addition to vinylketones. Since the often necessary activation of palladacycle catalysts by chloride ligand exchange using silver salts is not required in the present study, the reaction is operationally remarkably simple to conduct and might thus contribute to further advance the exploration of isoxazolinones in the pharmaceutical sciences.

Experimental Section

General procedure for the catalytic asymmetric Michael addition of isoxazol-5(4*H*)-ones **1** to vinylketones **2:** To the corresponding isoxazol-5(4*H*)-one (**1**, 1 equiv, 0.5 mmol) was added a solution of **[PPFIP-Cl]$_2$** (0.05–1.00 mol%) in CH_2Cl_2 (3.0 mL) and subsequently the corresponding vinylketone (**2**, 2 or 4 equiv, 1.0 or 2.0 mmol). After the reaction mixture had been stirred for 16 h at room temperature, the solvent was evaporated and the crude product was subjected to column chromatography (silica, petroleum ether/ethyl acetate: 4/1).

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