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Catalytic Asymmetric Chlorination of Isoxazolinones

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Organic compounds featuring a chlorine substituted stereocenter are frequently found in nature and are interesting for pharmaceutical applications and as synthetic building blocks. Catalytic methods to generate such stereocenters by C,H bond functionalization are still relatively rare. Here we report the first catalytic asymmetric chlorination of isoxazolinones, a synthetically and biologically interesting class of heterocycles, which can be considered as precursors for β-aminoacids. The title reaction was catalyzed with high enantioselectivity by a planar chiral ferrocene based palladacycle in high to excellent yields. It is showcased that the products are valuable for post-synthetic transformations. An S_N2 reaction proceeded with smooth inversion of the absolute configuration. The substitution product could then be transformed into an α-azido β-aminoacid derivative via a reductive, diastereoselective ring opening.

Introduction

Chlorine substituted stereocenters are found in a large number of natural products and pharmaceutically interesting compounds.[1] Thousands of natural products containing a chlorine or bromine atom bound at a stereocenter are known.[1] A prominent example is the cytotoxic polyhalogenated monoterpene halomon isolated from the red algae *Portieria hornemannii*.[2] It is one of only few substances showing activity against all 60 tumor cell lines of the National Cancer Institute.[3]

Enantiopure alkylchlorides are also valuable synthetic substrates for S_N2 type reactions. Even tertiary alkylchlorides were used for the construction of C–F, C–O, C–S, C–N, and C–C bonds at tetrasubstituted stereocenters, concomitant with an inversion of the absolute configuration.[4] Nevertheless, examples for S_N2 type reactions with such tertiary alkylchlorides are rare due to steric blocking of the reactive C–Cl bond.[4]

As a result of the utility of alkylchlorides, the construction of C–Cl bonds is an important strategy in organic synthesis and pharmaceutical industry.[4b] Nevertheless, the number of catalytic asymmetric methods forming Cl-substituted quaternary stereocenters is still quite limited. Next to desymmetrizations of prochiral alkylchlorides[5] and halofunctionalization of alkenes[6] there are mainly α-chlorinations of carbonyl derivatives.[4b] Substrates like enolizable β-ketoesters and oxindoles capable of two-point binding to a catalyst to create rigid reactive intermediates have been primarily reported.[4,7] In addition, asymmetric chlorinations of aldehydes were accomplished by enamine catalysis,[8] ketenes were chlorinated by Lewis base[9] and silyl enolethers by Lewis acid catalysis.[10]

In 2016, Wang et al. reported the catalytic asymmetric chlorination of pyrazolones, a biologically interesting class of heterocycles, using a cinchona alkaloid as Brønsted base catalyst at low reaction temperatures.[11] They also demonstrated the synthetic utility of the chlorination products in S_N2 reactions.

In contrast, for the structurally related isoxazolinones (systemic name: isoxazol-5-(4H)-ones)[12] catalytic asymmetric chlorinations have not been reported. These cyclic 5-membered oxime esters are also biologically interesting heterocycles[13] which, in addition, can be regarded as versatile β-aminoacid precursors.[14] Enantioselective chlorination of the isoxazolinones' 4-position might thus create new possibilities for the synthesis of enantiopure pharmacologically interesting β-aminoacid derivatives.[15]

Herein, we report the first catalytic asymmetric chlorination of isoxazolinones. It was achieved by a planar chiral palladacycle catalyst, which we recently also reported for the fluorination of this class of heterocycles.[14] In addition, an example is shown for the application in an S_N2 reaction and the post-synthetic transformation into a β-aminoacid derivative.

Results and Discussion

Substrate **1 a** was used for the development of the title reaction (Table 1) on a 0.1 mmol scale. The investigation was started by surveying the impact of different chlorination agents **A**–**E** using the chloride bridged planar chiral ferrocenyl palladacycle $[PPFIP–Cl]_2$[16] (PPFIP: 1′,2′,3′,4′,5′-pentaphenylferrocenyl imidazoline palladacycle) as precatalyst (entries 1–5). In previous work we found that ferrocene based imidazoline palladacycle catalysts are capable of efficiently activating pronucleophiles featuring C,N-π-bonds in α-position to a C,H-acidic C atom, such as isoxazolinones,[17,14] in asymmetric catalysis with high compatibility of functional groups.[18]

$[PPFIP–Cl]_2$ **C1** (2.5 mol%) was activated with AgOTs (5 mol%) by a chloride/tosylate exchange in the presence of

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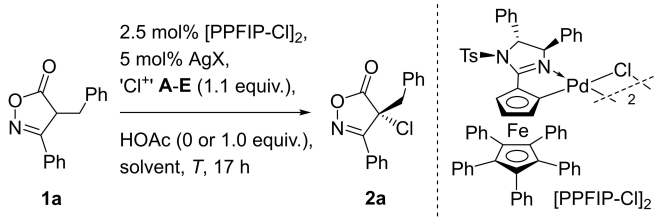
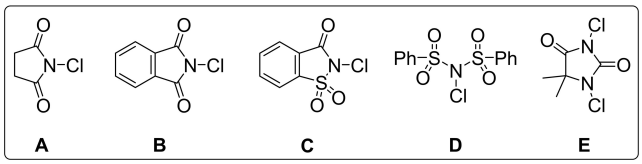
Table 1. Development of the title reaction.





#	'Cl$^+$'	X	T [°C]	Solvent	HOAc [equiv.]	Yield [%][a]	*ee* [%][b]
1	**A**	OTs	22	PhCl	–	99	44
2	**B**	OTs	22	PhCl	–	99	66
3	**C**	OTs	22	PhCl	–	47	26
4	**D**	OTs	22	PhCl	–	60	34
5	**E**	OTs	22	PhCl	–	99	10
6	**B**	OTs	0	PhCl	–	99	83
7	**B**	OTs	−10	PhCl	–	99	36
8	**B**	OTs	0	PhCl	+	99	86
9	**B**	OAc	0	PhCl	+	69	0
10	**B**	acac	0	PhCl	+	70	0
11	**B**	OTf	0	PhCl	+	99	71
12	**B**	–	0	PhCl	+	69	0
13	**B**	**OTs**	**0**	**CH_2Cl_2**	**+**	**99**	**96**
14	**B**	OTs	0	toluene	+	99	88
15	**B**	OTs	**0**	THF	+	10	75
16	**B**	OTs	0	MeCN	+	67	12

[a] Determined by ^{1}H-NMR of the crude product using mesitylene as internal standard. [b] Determined by HPLC.

MeCN prior to use. By that monomeric catalyst species are formed which should facilitate substrate binding.[16] Performing the reactions for 17 h at room temperature in chlorobenzene, moderate yields and low enantioselectivity were attained employing N-chlorosaccharin **C** and N-chlorobenzenesulfoneimide **D** as chlorination agents (Table 1, entries 3 & 4). In contrast, quantitative product yields were obtained for reagents N-chlorosuccinimide **A** (entry 1), N-chlorophthalimide **B** (entry 2) and 1,3-dichloro-5,5-dimethyl-hydantoin **E** (entry 5). The best enantioselectivity of 66% ee was noted with **B**. To increase enantioselectivity, the effect of lower reaction temperatures was studied. At 0 °C, the ee could be improved to 83% (entry 6), but a further temperature decrease resulted in lower ee's (entry 7). Acetic acid was then examined as additive, which might support the formation of an enol intermediate. By this change, the enantioselectivity was enhanced to 86% ee (entry 8). Different silver salts AgX were probed for catalyst activation, but both more (Lewis) basic anionic ligands X^- such as acetate (entry 9) and acetylacetonate (entry 10), but also less basic ones such as triflate (entry 11) did not provide any improvements. With the non-activated catalyst, racemic product was obtained (entry 12). No reaction occurred in the absence of a catalyst under these conditions. This suggests that [PPFIP–Cl]$_2$ is still acting as Lewis acidic catalyst, but not capable of controlling a face-selective attack of **B** at the assumed enol intermediate (see below).

Finally different solvents were applied. Among them toluene (entry 14) was found to be slightly more suitable than chlorobenzene, but the best solvent of those tested was dichloromethane. Under the conditions of entry 13, **2a** was formed in quantitative yield with an enantiomeric excess of 96% in a nearly quantitative yield. Under the same conditions, with the Lewis basic solvents THF (entry 15) and acetonitrile (entry 16) inferior results were obtained.

[PPFIP–Cl]$_2$ was also compared to other ferrocene based palladacycles from our portfolio (Table 2). The beneficial effect of the 1′,2′,3′,4′,5′-pentaphenylcyclopentadienide ligand is apparent from the results obtained with [FIP–Cl]$_2$ (entry 2),[16a,d,h] where the product was still formed in high yield, but with only moderate enantiomeric excess. Moreover, there is a positive influence of the imidazoline moiety in [PPFIP–Cl]$_2$ compared to the oxazoline moiety in [PPFOP–Cl]$_2$.[16d] Poor results in terms of yield and enantioselectivity were obtained with the bispalladacycle precatalyst [FBIP–Cl]$_2$ (entry 4).[19]

For [PPFIP–Cl]$_2$ it was found that quantitative yields are still possible with lower catalyst loadings, yet at the expense of a reduced enantioselectivity (entries 5 and 6). For the investigation of the scope of substrates, 2.5 mol% of [PPFIP–Cl]$_2$ was thus used (Table 3). The impact of several other residues R^2 than

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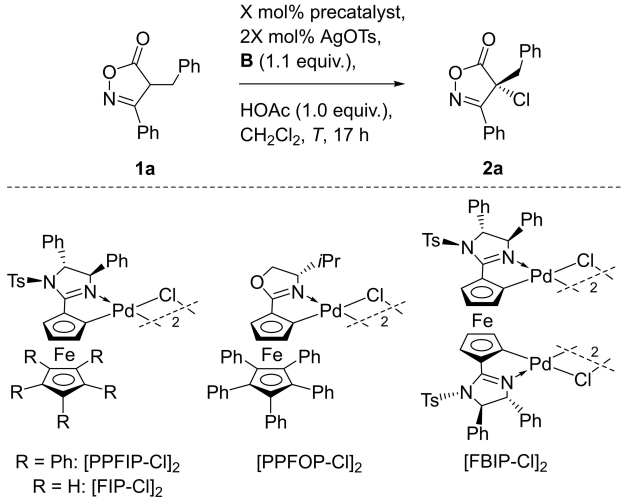
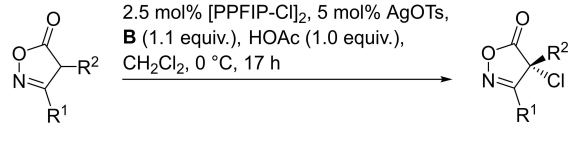
Table 2. Catalyst Investigation.



#	Precatalyst	X	Yield [%][a]	*ee* [%][b]
1	[PPFIP–Cl]$_2$	2.5	99	96
2	[FIP–Cl]$_2$	2.5	92	54
3	[PPFOP–Cl]$_2$	2.5	95	34
4[c]	[FBIP–Cl]$_2$	2.5	41	33
5	[PPFIP–Cl]$_2$	2.0	99	86
6	[PPFIP–Cl]$_2$	1.5	99	83

[a] Determined by ^{1}H-NMR of the crude product using mesitylene as internal standard. [b] Determined by HPLC. [c] 10 mol% of AgOTs was used for catalyst activation.

Table 3. Investigation of the Substrate Scope.



#	1/2	R^1	R^2	Yield [%][a]	*ee* [%][b]
1	**a**	Ph	Bn	98	96
2	**b**	Ph	2-naphthyl–CH_2	96	97
3	**c**	Ph	4-Br–C_6H_4–CH_2	86	91
4	**d**	Ph	4-NC–C_6H_4–CH_2	93	92
5	**e**	Ph	4-OMe–C_6H_4–CH_2	85	90
6	**f**	Ph	4-Me–C_6H_4–CH_2	88	88
7	**g**	Ph	2-Cl–C_6H_4–CH_2	96	77
8	**h**	Ph	Me	88	94
9	**i**	Ph	*n*-Pr	92	95
10	**j**	Ph	Allyl	93	73
11	**k**	Ph	Ph	82	89
12	**l**	4-Cl–C_6H_4	Bn	95	95
13	**m**	4-MeO–C_6H_4	Bn	86	87
14	**n**	4-Cl–C_6H_4	Me	90	89

[a] Yield of isolated product. [b] Determined by HPLC.

benzyl (entry 1) was studied. With a 2-naphthylmethyl group the highest ee was attained (97%, entry 2). In addition, the effect of several functionalized benzyl moieties was examined. *para*-Substituents on the aryl rings were all well tolerated for electron donors and acceptors (entries 3–6). *ortho*-Substitution also allowed for an excellent yield, but the ee was decreased (entry 7).

Next to the benzylic residues, products with alkyl groups R^2 were formed in high yields and with high enantioselectivity (entries 8 & 9). With an allyl residue the ee was decreased to 73%, while the product yield was still high (entry 10). In addition to these substrates with aliphatic groups R^2, the method can be applied to those bearing aromatic groups directly bound to the enolizable C atom, as is exemplified in entry 11. Also in this case, yield and enantioselectivity were high.

Moreover, it was found that variations of the aromatic residues R^1 at the imino C atom are possible (entries 12–14). However, as a limitation we found that substrates with a simple alkyl group R^1 such as methyl permitted only poor enantioselectivity, whereas the product yields were still good (not shown).

The absolute configuration of **2a** could be determined as (*R*) by X-ray single crystal structure analysis (Figure 1),[20] which is in agreement with the configurational outcome for further functionalizations of this substrate class catalyzed by a PPFIP catalyst.

We assume that the reaction mechanism is very similar to those previously suggested for our 1,4 additions and fluorinations of isoxazolinones, applying the same type of catalyst.[14,17,21] It should involve coordination of the substrate by its N-atom to the azaphilic Pd(II) center thus triggering substrate enolization, that might be facilitated by HOAc. Due to the acidic conditions we think that the formation of an enolate intermediate is unlikely in this method.[22] The stereochemical outcome might be explained by our previously reported working models.[14,17]

To showcase the synthetic value of the reaction products, we studied the option of an S_N2 displacement. Prior to use, the chlorination product **2a** was crystallized in order to get almost enantiopure material. In analogy to the work by Wang using pyrazolones,[11] use of NaN_3 in dry DMSO delivered the substitution product in high yield and with a negligible level of racemization (98% ee). The x-ray crystal structure analysis of **3**[20] confirms an S_N2 mechanism, because an inversion of the stereochemical configuration was determined (see box in Scheme 1).

A reductive ring opening of the isoxazolinone ring was achieved under the conditions which we recently reported for fluorinated isoxazolinones. Under substrate control a diastereomeric ratio of 4:1 was found. Oxidation of the primary alcohol

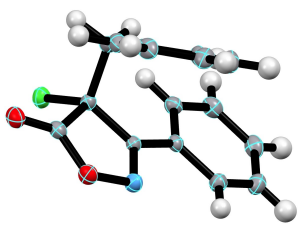


Figure 1. X-ray crystal structure analysis of **2a**.

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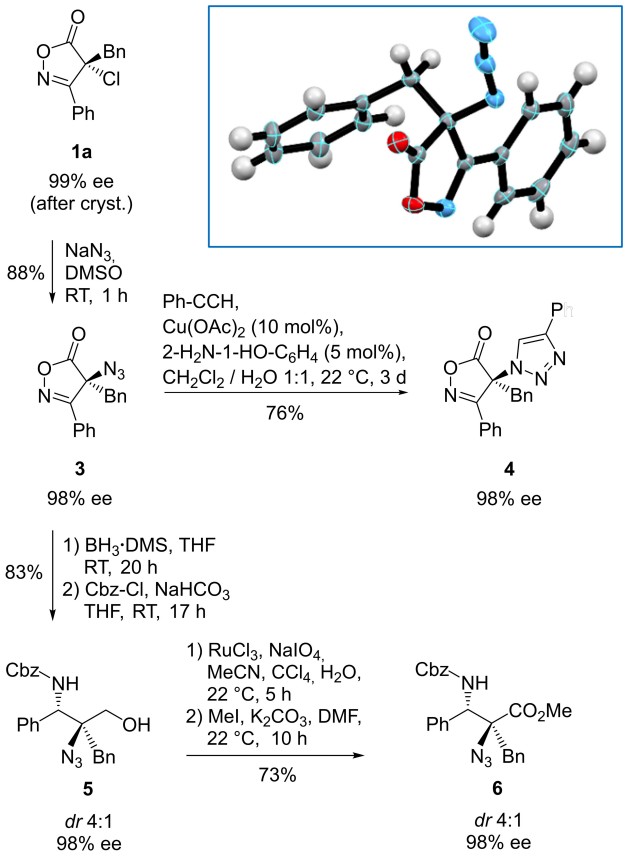

Scheme 1. Post-synthetic transformations of **2a**, including the synthesis of an α-azido β-aminoacid derivative **6**, and an X-ray crystal structure analysis of substitution product **3** (see box).

function followed by esterification gave the α-azido β-aminoacid derivative **6** as synthetically interesting building block. In addition, substitution product **3** was further employed for a copper catalyzed azide/alkyne cycloaddition to form 1,2,3-triazole **4**.

Conclusion

In conclusion, we have reported the first catalytic asymmetric chlorination of isoxazolinones. This was enabled by a planar chiral palladacycle catalyst derived from a 1′,2′,3′,4′,5′-pentaphenylferrocenyl imidazoline ligand. The products were formed with high enantiomeric excess and in good to excellent yields. One chlorination product was exemplarily used for a nucleophilic substitution reaction with NaN_3, which proceeded with almost complete inversion of the absolute configuration, thus pointing to an S_N2 type reaction of the tertiary chloride. An interesting α-azido β-aminoacid derivative could be prepared by a diastereoselective ring opening reaction. These studies further emphasize the value of isoxazolinones for asymmetric synthesis.

Experimental Section

General procedure for the asymmetric chlorination of isoxazolinones: A solution of the corresponding isoxazolinone **1** (1.0 equiv.), catalyst ($[PPFIP–Cl]_2$ (2.5 mol%) activated by AgOTs (5 mol%)), N-chlorophthalimide B (1.1 equiv.) and HOAc (1.0 equiv.) in chlorobenzene (0.2 M) was stirred at 0 °C for 17 h. The solution was then directly subjected to column chromatography (PE/EE, 20:1) to isolate the product.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Aminoacids · Asymmetric catalysis · Ferrocene · Nucleophilic substitution · Palladacycles

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