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COMMUNICATION

Phase-transfer-catalysed Asymmetric Synthesis of 2,2-Disubstituted 1,4-Benzoxazin-3-ones

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1,4-Benzoxazin-3-one is a scaffold which is found in a variety of biologically active molecules. Because of its unique structure and drug-like activities, 1,4-benzoxazin-3-ones have been widely used in drug discovery. However, just a few methods have been developed to access these molecules by catalytic asymmetric synthesis. We report herein the phase-transfer-catalysed asymmetric alkylation of 2-aryl-1,4-benzoxazin-3-ones as a new way for the highly enantioselective synthesis of 2,2-disubstituted 1,4-benzoxazin-3-ones.

1,4-Benzoxazin-3-ones are a class of compounds which appear in a variety of biologically active molecules as represented by a renin inhibitor developed by Pfizer (Fig. 1).[1,2] The structure is wide-spread not only within synthetic compounds but also within natural products such as rifamorpholine A, which was recently isolated and exhibited activity as potential antibiotic.[3]

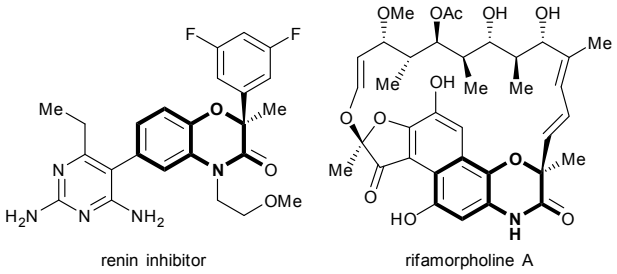

Fig. 1 Biologically active 2,2-disubstituted 1,4-benzoxazin-3-ones.

Because of these interesting properties, synthetic methods to construct 1,4-benzoxazin-3-ones have been well studied.[4,5] However, despite the existence of a stable stereocenter at the 2-position in form of a 2,2-disubstituted 1,4-benzoxazin-3-one, only a few catalytic methods to forge this stereogenic center in an enantiomerically enriched way have been developed to date.[6-9] Building on the acidity of the hydrogen atom at the 2-position of 2-mono-substituted benzoxazinones, we surmised that the ability of a phase-transfer catalyst which enables an enantioselective alkylation under basic conditions is suitable for the realisation of such a transformation (Fig. 2).[10]

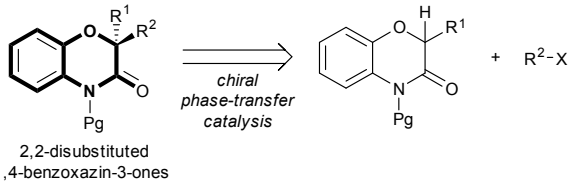

Fig. 2 Synthesis of 2,2-disubstituted 1,4-benzoxazin-3-ones by phase-transfer catalysis.

We report herein the chiral phase-transfer-catalysed alkylation of a range of 1,4-benzoxazin-3-ones to give enantio-enriched 2,2-disubstituted 1,4-benzoxazin-3-ones. The alkylation worked efficiently with 2-aryl substituted benzoxazinones by the use of a binaphthyl-based phase-transfer catalyst bearing N,N-diisopentyl groups as a distinctive feature.

The initial optimisation was commenced with the identification of a proper N-protecting group for 2-phenyl benzoxazinone, which would affect the reactivity and selectivity of the reaction, using phase-transfer catalyst **1a**, benzyl bromide and powdered KOH as base in toluene (Table 1). Attachment of a Boc protecting group (**4a**) was found to be promising and the benzylated product **5aa** could be isolated in 89% yield with 83% ee at 0 °C (entry 1). Benzoxazinone with a N-Cbz group was converted to the corresponding product with lower enantioselectivity (entry 2). The stability of the substrate under strongly basic conditions must be taken into consideration, as evidenced by the N-benzoyl substrate, with which facile hydrolysis of the C-N bond was observed (entry 3). On the other hand, N-benzyl 1,4-benzoxazin-3-one gave only trace amount of the product (entry 4), underlying the necessity of an electron-withdrawing N-protecting group. In addition,

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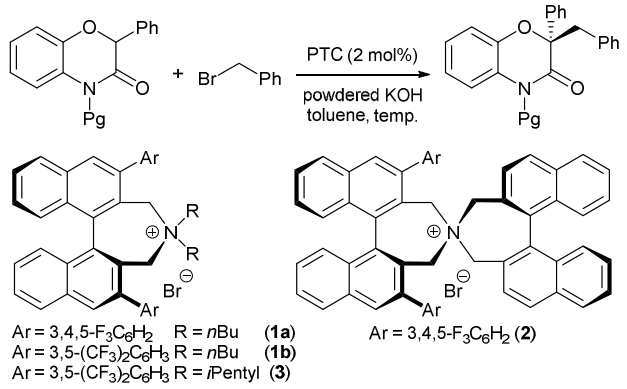
use of solvents more polar than toluene resulted in rapid decomposition of the substrate and lower enantioselectivity even with the N-Boc substrate (data not shown).

We then turned our attention to the optimisation of the catalyst structure. Varying the 3,3'-aryl moieties of catalyst **1a** revealed that most of the screened aryl groups had no positive effect on the selectivity (data not shown) except for **1b** with which a slight increase in selectivity was observed (entry 5). Attempts to achieve a higher enantioselectivity by use of more complex chiral phase-transfer catalysts bearing two binaphthyl units such as **2** also failed (entry 6). Further catalyst optimisations at a lower temperature led us to the adjustment of the N-alkyl chain, in which the N,N-diisopentyl quaternary ammonium salt **3** was found to be the most effective catalyst yielding the product in 96% ee at –25 °C (entries 7-9). The increased yield at lower temperature is presumably due to the suppression of the substrate decomposition.

Table 1. Optimisation of the reaction conditions[a]

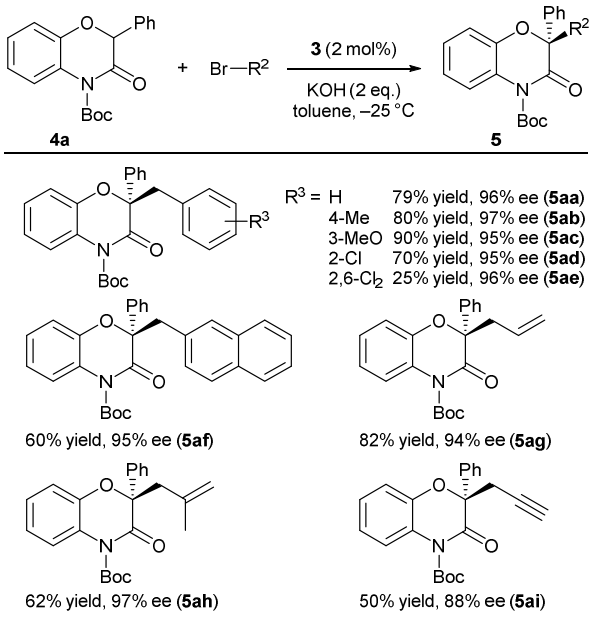


entry	Pg	PTC	temp. (°C)	% yield[b]	% ee[c]
1	Boc (**4a**)	**1a**	0	87 (**5aa**)	83
2	Cbz	**1a**	0	<50	53
3	Bz	**1a**	0	-	-
4	Bn	**1a**	0	8	25
5	Boc	**1b**	0	83	84
6	Boc	**2**	0	57	69
7[d]	Boc	**1b**	–20	68	86
8[d]	Boc	**3**	–20	58	89
9[d,e]	Boc	**3**	–25	79	96

[a] Performed with 2-phenyl benzoxazinone (0.10 mmol), benzyl bromide (0.50 mmol), PTC (2 mol%) and KOH (0.15 mmol) in toluene (1 mL). [b] Isolated yield. [c] Ee determined by chiral HPLC. [d] Performed with KOH (0.20 mmol). [e] Performed with benzyl bromide (0.25 mmol).

With the optimised reaction conditions in hand, we examined the scope of this transformation using a variety of benzylic and allylic bromides (Table 2). As for benzylic bromides, the reaction proceeded with high enantioselectivities regardless of the substitution pattern and electronic properties (**5aa**-**5ad**). In the case of 2,6-dichlorobenzyl bromide, the reaction became sluggish while the enantioselectivity remained very high (**5ae**). In addition, 2-naphthylmethyl bromide was also a viable reactant with which compound **5af** was obtained in 95% ee. In addition to benzylic bromides, allyl bromide and 2-methylallyl bromide were applied as representative allylic bromides and in both cases the products **5ag** and **5ah** were obtained with high enantioselectivities. The reaction with propargyl bromide resulted in a slightly lower yield and enantioselectivity (**5ai**).

Table 2. Alkyl bromide substrate scope[a-c]



[a] Performed with **4a** (0.10 mmol), alkyl bromide (0.25 mmol), **3** (2 mol%) and KOH (0.20 mmol) in toluene (1 mL). [b] Isolated yield. [c] Ee determined by chiral HPLC.

We then shifted the focus to the substrate scope with respect to the benzoxazinone template (Table 3). Expectedly, the 2-aryl moiety of benzoxazinone affected the reactivity substantially. For instance, 4-methoxyphenyl substituted benzoxazinone showed lower reactivity likely due to the attenuated acidity of the substrate while the high enantioselectivity was sustained (**5ba**). On the contrary, substrates with a halogenated aromatic ring were well tolerated, giving the products **5ca**-**5fa** in good yields and enantioselectivities. Attachment of an ortho-substituent to the aromatic ring completely shut down the alkylation because of steric hindrance around the reaction site (data not shown). The absolute configuration of alkylation product was established to be (*R*) by X-ray analysis of compound **5ha**.[11]

Afterwards, in consideration that the 6-substituent of benzoxazinones is important for biological activities in many cases,[1,2] we examined substrates bearing a substituent at the 6-position of the heterocycle core. Methyl, methoxy, bromo and fluoro substituted benzoxazinones all reacted smoothly and the corresponding 2,2-disubstituted benzoxazinones **5ia**-**5la** were obtained in good yields and high enantioselectivities. It should be noted that, in the case of **5ia**, **5ka** and **5la**, the instability of the substrates under strong basic conditions led

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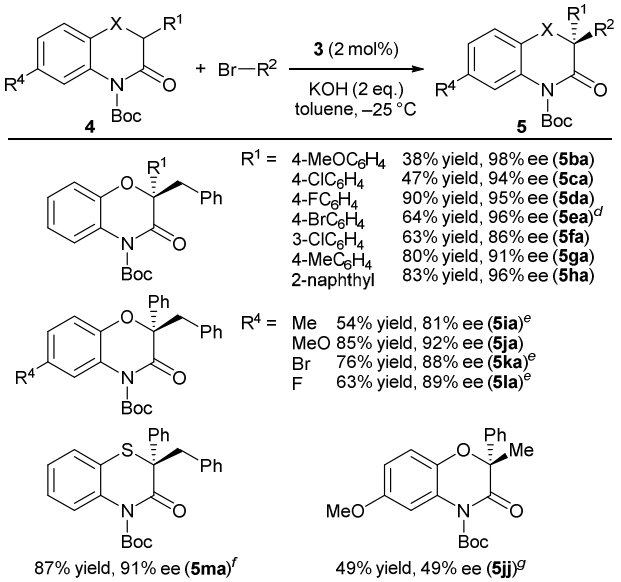
us to implement the reactions using K_3PO_4 as a weaker base and mesitylene as a less polar solvent.

The asymmetric alkylation was also applicable to a sulphur analogue, benzothiazinone, with which compound **5ma** was obtained in a comparable yield and enantioselectivity using a slightly higher catalyst loading and mesitylene as solvent.

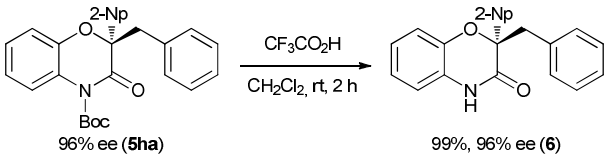
With respect to the renin inhibitor developed by Pfizer (Fig. 1), we attempted to incorporate a methyl group by use of dimethyl sulfate as electrophile. The reaction with 6-methoxy benzoxazinone resulted in a modest result of 49% yield and 49% ee (**5jj**). The major issue of this methylation, other than the enantioselectivity, is the O-alkylation of the substrate which deterred the yield of the desired product.[12] It should be noted that the use of less reactive alkyl halides resulted in traces of product under our reaction conditions.

Table 3. Benzoxazinone substrate scope[a-c]



[a] Performed with **4** (0.10 mmol), benzyl bromide (0.25 mmol), **3** (2 mol%) and KOH (0.20 mmol) in toluene (1 mL). [b] Isolated yield. [c] Ee determined by chiral HPLC. [d] –35 °C [e] Benzyl bromide (0.40 mmol), **3** (2 mol%) and K_3PO_4 (1.00 mmol) in mesitylene (1 mL). [f] **3** (5 mol%) in mesitylene (1 mL) at –10 °C. [g] **3** (5 mol%) and Me_2SO_4 (3.00 mmol).

Deprotection of the Boc group was achieved by treating the product with trifluoroacetic acid in dichloromethane in quantitative yield and without loss of the enantioselectivity (Scheme 1).



Scheme 1. Deprotection of the N-Boc group.

In conclusion, we developed the catalytic asymmetric synthesis of 2,2-disubstituted 1,4-benzoxazin-3-ones by use of chiral phase-transfer catalysis. The reaction was applicable to a variety of 2-aryl substituted 1,4-benzoxazin-3-ones with benzylic, allylic and propargylic bromides serving as electrophiles. While further optimisation is needed, methylation could also be achieved in one example.

This work was partially supported by a Grant-in-Aid for Scientific Research from MEXT (Japan). M.P. thanks Deutsche Forschungsgemeinschaft (DFG) for postdoctoral fellowship.

Conflicts of interest

There are no conflicts to declare.

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11 CCDC 1840492 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.
12 Our investigations around the alkylation of the benzoxazine core revealed the undesired O-alkylation instead of C-alkylation as a persistent obstacle and reason for diminished yields. Catalyst structure as well as steric and electronic modifications of heterocyclic core influenced this selectivity. Our optimized catalyst **3** not just gave the best enantioselectivities but also minimised the amount of O-alkylation product to less than 5% in most cases.

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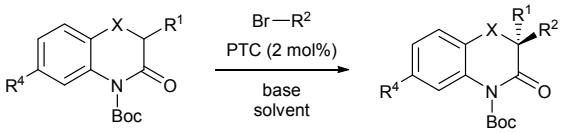

up to 98% ee

The phase-transfer-catalysed alkylation of 2-aryl-1,4-benzoxazin-3-ones was developed as a way for the synthesis of enantioenriched 2,2-disubstituted 1,4-benzoxazin-3-ones.

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