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3-Aminoquinazolinones as chiral ligands in catalytic enantioselective diethylzinc and phenylacetylene addition to aldehydes

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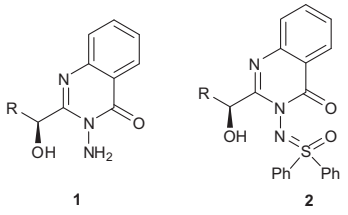
ABSTRACT

A series of readily known enantiomerically pure 3-aminoquinazolinones **1a–d** were synthesised from easily accessible chiral pool α-hydroxy acids and α-amino acids in only four steps without any requirement of chromatography. These quinazolinones were examined as chiral ligands for catalytic enantioselective diethylzinc and phenylacetylene additions to aldehydes. For enantioselective alkylations, the effects of temperature, solvent, diethylzinc and ligand criteria were analysed, and the desired chiral alcohols were obtained in up to 86% ee. 3-Aminoquinazolinones **1a–d** were also shown to be very useful ligands in enantioselective alkynylations of aldehydes. Based upon the optimised conditions, the corresponding propargylic alcohols were obtained in up to 94% ee.

1. Introduction

Catalytic asymmetric synthesis has become one of the most attractive areas of research and gives enantioenriched or enantiopure compounds in large quantities by using a small amount of catalyst.[1] Among the asymmetric reactions, organozinc additions to aldehydes have attracted considerable attention to meet the demands of organic synthons both in academia and in industry.[2] In chiral ligand families, the nitrogen containing ones such as amino alcohols,[3–7] arylimines,[8,9] pyridyl alcohols,[10,11] oxazolines,[12,13] quinolins,[14–16] quinazolines and quinazolinones[17,18] and their derivatives[19–23] have been widely used in this manner in recent years.

In our previous work, chiral sulfoximine derivatives **2a–d** from 3-aminoquinazolinones **1a–d** were synthesised while the catalytic activities of sulfoximines have been tested in enantioselective alkylations of aldehydes.[24] The related alcohols were obtained with up to 92% ee. The lead tetraacetate oxidations of 3-aminoquinazolinones **1a–d** are also well known as aziridinating agents for alkenes with different electron demands, for example, styrene and methyl acrylate.[25–27] High reagent and substrate-controlled diastereoselective aziridination is possible where a stereogenic centre is present.[28] 3-Aminoquinazolinones **1a–d** with a stereogenic centre at its 2-position has an environment similar to 1,3-aminoalcohols. Therefore, we herein anticipated the possibility of using the known 3-aminoquinazolinones **1** not as aziridinating agents but also as chiral ligands in the enantioselective phenylacetylene and diethylzinc additions to aldehydes (Fig. 1).



1a; R = Me, **1b**; R = ^{i}Pr, **1c**; R = ^{t}Bu, **1d**; R = Ph

Figure 1.

2. Results and discussions

3-Aminoquinazolinones **1a–d** were readily prepared in four steps using known procedures[29–32] starting from enantiomerically pure L-lactic acid **3a**, L-valine **3b**, L-*t*-leucine **3c** and L-mandelic acid **3d** (Scheme 1).[24] Herein we tested these chiral molecules **1a–d** as ligands in catalytic asymmetric diethylzinc and phenylacetylene additions to aldehydes.

At first, we examined Et_2Zn (3 equiv, 1 M in hexane) addition to benzaldehyde for the catalytic process using 10 mol % 3-aminoquinazolinones **1a–d** at 0 °C and toluene as the solvent. Since 3-aminoquinazolinone **1c** had a better differentiated group on

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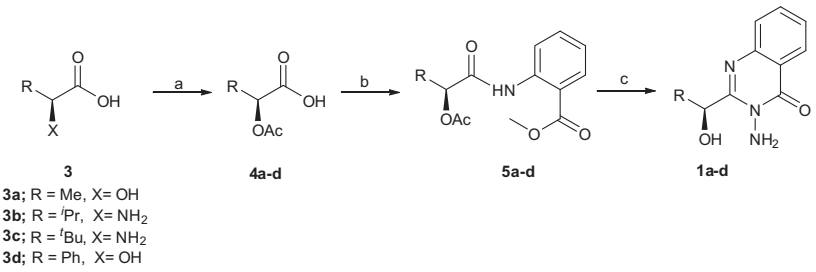


Scheme 1. Synthesis of the quinazolinone alcohols **1a–d**. Reagents and conditions: (a) for **3a** and **3d**: AcCl (4.0 equiv), RT; for **3b** and **3c**: $NaNO_2$ (4.0 equiv), AcOH, RT; (b) $SOCl_2$ (3.0 equiv), DMF (cat.), RT; (c) methyl 2-aminobenzoate (2.2 equiv), Et_2O, RT; (d) hydrazine (5.0 equiv), EtOH, 150 °C.

the stereogenic centre among the quinazolinones, it afforded a favourable enrichment of the products both in terms of enantiomeric excess and yield (Table 1, entry 4). While 3-aminoquinazolinones **1a** and **1b** yielded 1-phenyl-1-propanol in moderate selectivity (Table 1, entries 1 and 2), 3-aminoquinazolinone **1d** did not allow the formation of any product ee (Table 1, entry 3). We then continued to optimise the reaction conditions for solvent, temperature, Et_2Zn equivalent and amount of ligand. In order to choose an appropriate solvent for the reaction condition, a series of solvents commonly used in alkylation reactions such as toluene, hexane, Et_2O, THF, CH_2Cl_2 and TBME were screened. It was observed that the solvent influenced the enantioselectivity and product formation significantly. Among the solvents used in the reaction, toluene remained the best in terms of product enantioselectivity (71% ee). The ee and yield were obtained with very low values when the reaction was conducted in the presence of hexane (7% ee, 43% yield), THF (11% ee, 15% yield) or CH_2Cl_2 (32% ee, 54% yield). On the other hand, when Et_2O or TBME was used as the solvent, the enantioselectivity of the products was moderate with 55% ee and 60% ee. A decrease in temperature from 0 to −20 °C (Table 1, entry 6) led to an increase in enantioselectivity from 71% ee to 83% ee. However, lowering the reaction temperature to −40 °C, lowered the product both in terms of enantioselectivity and yield (Table 1, entry 7). Additionally, the amount of Et_2Zn from 3 to 2 equiv (Table 1, entry 9) led to a slight increase in enantioselectivity (85% ee). The amount of ligand was reduced sequentially from 10% to 5% and then 2%, leading to a decrease in enantiomeric excess (Table 1, entries 10 and 11). Eventually, the best results (85% ee and 95% yield) were found when using 2 equiv of Et_2Zn, at −20 °C and 10 mol % ligand.

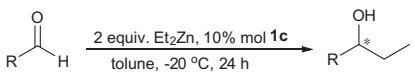
The optimised conditions (2 equiv Et_2Zn, at −20 °C and 10 mol % ligand) were then applied to a variety of aryl substituted aldehydes. As can be seen in Table 2, the chiral secondary alcohols **6a–h** were achieved with good to excellent isolated yields (80–99%) except for pyridine-2-carboxaldehyde (58%). Benzaldehyde, *p*-tolualdehyde and *m*-methoxybenzaldehyde were converted into their respective chiral alcohols with good enantioselectivities (Table 2, entries 1, 4 and 5). Moderate product ees were obtained from *o*-methoxybenzaldehyde and cinnamaldehyde (Table 2, entries 3 and 7); we were unable to determine any reason as to why *o*-chlorobenzaldehyde gave the lowest product ee of 3%. However, it was unsurprising that the pyridine-2-carboxaldehyde derived alcohol gave poor enantioselectivity (19% ee), which was probably due to zinc complexing through the pyridine nitrogen and the hydroxyl oxygen formed during reaction and self-catalysed.

Table 1
3-Aminoquinazolinones **1a–d** catalysed diethylzinc addition to benzaldehyde

Entry	Ligand (%)	Temp. (°C)	ee[a] (%)	Yield[b] (%)
1	**1a** (10)	0	50	85
2	**1b** (10)	0	43	78
3	**1d** (10)	0	0	67
4	**1c** (10)	0	71	96
5	**1c** (10)	RT	49	98
6	**1c** (10)	−20	83	93
7	**1c** (10)	−40	72	65
9	**1c** (10)[c]	−20	85	95
10	**1c** (5)	−20	79	95
11	**1c** (2)	−20	60	63

[a] Determined by chiral GC analysis (β-Dex column).
[b] Isolated yields.
[c] 2 equiv Et_2Zn used.

Table 2
Results of the enantioselective addition of Et_2Zn to aldehydes promoted by **1c**



Entry	Aldehyde	Product	ee[a] (%)	Yield[c] (%)	Configuration[d]
1	Benzaldehyde	**6a**	85	95	(*S*)
2	*o*-Chlorobenzaldehyde	**6b**	3	93	(*S*)
3	*o*-Methoxybenzaldehyde	**6c**	71	80	(*S*)
4	*m*-Methoxybenzaldehyde	**6d**	80	99	(*S*)
5	*p*-Tolualdehyde	**6e**	86	84	(*S*)
6	1-Naphthylaldehyde	**6f**	34	85	(*S*)
7	Cinnamaldehyde	**6g**	67[b]	99	–
8	Pyridine-2-carboxaldehyde	**6h**	19	58	–

[a] Determined by chiral GC analysis (β-Dex column).
[b] Determined by chiral HPLC (Chiralcel OD-H).
[c] Isolated yields.
[d] The absolute configurations of the products were assigned according to the literature.[24]