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Full Paper

Copper-Catalyzed 1,4-Addition | *Very Important Paper* |

# Conjugate Addition Routes to 2-Alkyl-2,3-dihydroquinolin-4(1*H*)-ones and 2-Alkyl-4-hydroxy-1,2-dihydroquinoline-3-carboxylates

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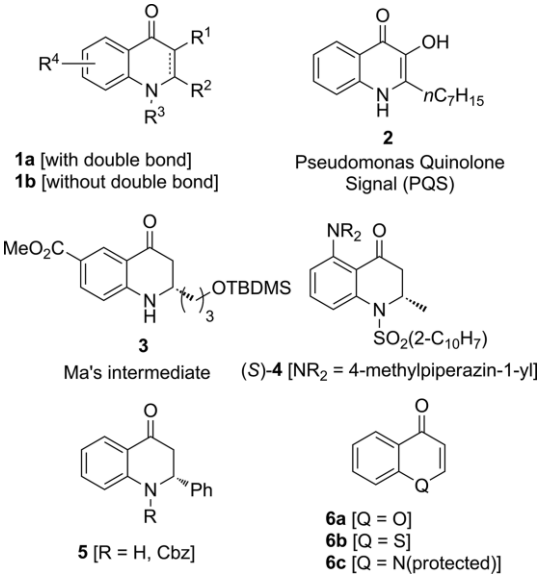
**Abstract:** Under CuBr•SMe2/PPh3 catalysis (5/10 mol-%) RMgCl (R = Me, Et, *n*Pr, CH=$CH_2$, *n*Bu, *i*Bu, $nC_5H_{11}$, $cC_6H_{11}$, Bn, $CH_2$Bn, $nC_{11}H_{23}$) readily (–78 °C) undergo 1,4-addition to Cbz or Boc protected quinolin-4(1*H*)-ones to provide 2-alkyl-2,3-dihydroquinolin-4(1*H*)-ones (14 examples, 54–99 % yield). Asymmetric versions require $AlEt_3$ to Boc-protected ethyl 6-substituted 4(1*H*)-quinolone-3-carboxylates (6-R group = all halogens, *n*/*i*/*t*-alkyls, $CF_3$) and provide 61–91 % yield, 30–86 % *ee*; any halogen, Me, or $CF_3$ provide the highest stereoselectivities (76–86 % *ee*). Additions of $AlMe_3$ or $Al(nC_8H_{17})_3$ provide ≈ 45 and ≈ 75 % *ee* on addition to the parent (6-R = H). Ligand (S)-(BINOL)P–N(CHPh$_2$)($cC_6H_{11}$) provides the highest *ee* values engendering addition to the Si face of the 4(1*H*)-quinolone-3-carboxylate. Allylation and deprotection of a representative 1,4-addition product example confirm the facial selectivity (X-ray crystallography).

## Introduction

Quinolone sub-structure cores **1a** and their dihydro-analogues **1b** (Scheme 1) constitute privileged starting materials in medicinal and natural product chemistry. The former core has been a lynchpin in antibiotic development for more than 50 years,[1] most recently in quorum sensing approaches, e.g. the moderation of bacterial activity engendered by species such as **2**.[2] The latter core **1b** has been deployed in the syntheses of a range of natural and biologically active molecules, for example Ma's intermediate (**3**),[3] used in the synthesis of martinellic acid (a natural Bradykinin antagonist); and in the related **4**; active at 7 nM towards 5-HT6 serotonin receptors.[4] Compounds **3**–**4** are exemplary of the recent move to explore $sp^3$ rich heterocycles in medicinal chemistry.[5] Such concepts are poorly explored for dihydroquinolones, with **5** being the only common "model compound" encountered, providing significant stereoselectivities for *aryl* additions and being attained by either Rh-[6] or Pd-catalysed[7] ArM (M = ZnCl, $BAr_3$) addition providing **6c** (R = aryl) in 40–99+% *ee*, or by a variety of organocatalytic closures (0–99+% *ee*) leading to the same core but from different 2-aminochalcone and related intermediates.[8] As both these approaches do not presently allow access to more biologically interesting $sp^3$ substituents (e.g. **3**–**4** etc.) we sought to study presently less explored *alkyl* organometallic additions to **6c**. This seemed potentially profitable as catalytic enantioselective 1,4-alkyl additions to related **6a**–**b** (Y = O, S with R = alkyl) are already known (9–96 % *ee*).[9]




Scheme 1. Quinolone and derived dihydro-analogues of relevance to this publication.

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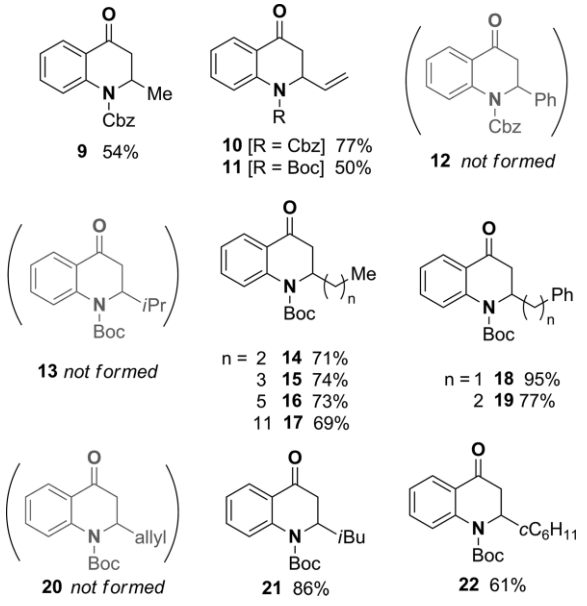
## Results and Discussion

### Additions to Protected Quinolin-4(1*H*)-ones (7)

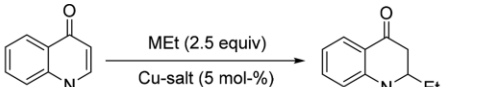
The protected acceptors **7a**–**d** (within Table 1) are readily accessible from commercial quinolin-4(1*H*)-one, which is itself also available from 2-nitroacetophenone via standard heterocyclic chemistry.[10] As stoichiometric copper reagents had already been used in copper-promoted additions to **7a** (for aza analogues of the natural product Wrightiadione.[11]), we tested this substrate under catalytic conditions, but it proved too deactivated to react. The more electron deficient **7b** still performed poorly with $ZnEt_2$ or $AlEt_3$, under typical conjugate addition conditions. Runs 1–2 were the best outcomes we could attain from a range of conditions. As we could readily confirm that the stoichiometric cuprate MgBr[$CuEt_2$] readily added to **7b** in THF upon reaction at –78 to –20 °C affording a 65 % isolated yield of **8b** we trialled catalytic versions of this chemistry. In the absence of added ligands conversions were modest in THF (Run 3), and worse upon addition of $Et_2O$ (Run 4) due to the insolubility of **7b** in this solvent. Remarkably, although **7b** is also insoluble in 2-MeTHF at low temperature, this solvent produced a very rapid 1,4-addition (within 5 min), which could be somewhat further promoted by simple phosphorus ligand addition (Runs 5–7). Simply increasing the overall reaction time to 1 h led to complete conversion in both the Cbz and Boc protected quinolin-4(1*H*)-ones (**7b**–**c**) (Runs 8–9) while the methyl carbamate (**7d**) was inferior (Run 10). By employing these optimal conditions of Table 1 we could show the synthetic scope of the 2-MeTHF reaction conditions (Scheme 2); which contains compounds of clear synthetic and biological utility. Species **8b**–**c** and **9** have only been mentioned passingly in alternative methodology aimed at biologically active targets,[12] while all other isolated examples in Scheme 2 are novel. Certain limitations were noted in the chemistry of Scheme 2: (i) the lowest yields were associated with addition of MeMgX to **7b** while **7c** did not participate in the same reaction; (ii) the catalytic reaction is sensitive to α-branching in the Grignard (e.g. *i*PrMgBr and PhMgBr do not react and $cC_6H_{11}MgBr$ give a reduced yield); (iii) Allyl Grignard did not participate in the reaction.




Scheme 2. Scope and limitations of CuBr·$SMe_2$/$PPh_3$ catalysed 1,4 Grignard addition to acceptors **7**. Isolated yields.

Having established viable catalysis, we turned our attention to the potential for an asymmetric version. Using the conditions of Scheme 2 but truncating the reaction time to just 2.5 minutes for the EtMgBr 1,4-addition to **7b** is instructive. In the absence of any added ligand CuBr·$SMe_2$ (5 mol-%) a 35 % conversion to **8b** is already realised. In the presence the same copper loading and conditions, but with added phosphine ligands

Table 1. Optimisation of EtMgBr addition to *N*-protected quinolin-4(1*H*)-ones **7**.




| 7 | R |
|---|---|
| **7a** | Me |
| **7b** | Cbz |
| **7c** | Boc |
| **7d** | $CO_2Me$ |

| 8 | R |
|---|---|
| **8a** | Me (*not formed*) |
| **8b** | Cbz |
| **8c** | Boc |
| **8d** | $CO_2Me$ |

| Run | 7 | MEt | Cu-source | Ligand | Solvent | Temp (°C) | Time | Conv. (%)[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | **7b** | $ZnEt_2$ | $Cu(OAc)_2$ | $P(OPh)_3$ | THF | -10 | 12 h | – |
| 2 | **7b** | $AlEt_3$ | $Cu(OTf)_2$ | $P(OPh)_3$ | THF | -10 | 18 h | <25 |
| 3 | **7b** | EtMgBr | CuBr·$SMe_2$ | – | THF | -50 to -10 | 1.5 h | 34 |
| 4 | **7b** | EtMgBr | CuBr·$SMe_2$ | – | THF/$Et_2O$ (1:1) | -78 to -20 | 1 h | 31 |
| 5 | **7b** | EtMgBr | CuBr·$SMe_2$ | – | 2-MeTHF | -78 | 5 min | 75 |
| 6 | **7b** | EtMgBr | CuBr·$SMe_2$ | $P(OPh)_3$ | 2-MeTHF | -78 | 5 min | 88 |
| 7 | **7b** | EtMgBr | CuBr·$SMe_2$ | $PPh_3$ | 2-MeTHF | -78 | 5 min | 96 |
| 8 | **7b** | EtMgBr | CuBr·$SMe_2$ | $PPh_3$ | 2-MeTHF | -78 | 1 h | **>99**[b] |
| 9 | **7c** | EtMgBr | CuBr·$SMe_2$ | $PPh_3$ | 2-MeTHF | -78 | 1 h | **>99**[c] |
| 10 | **7d** | EtMgBr | CuBr·$SMe_2$ | $PPh_3$ | 2-MeTHF | -78 | 1 h | 78 |

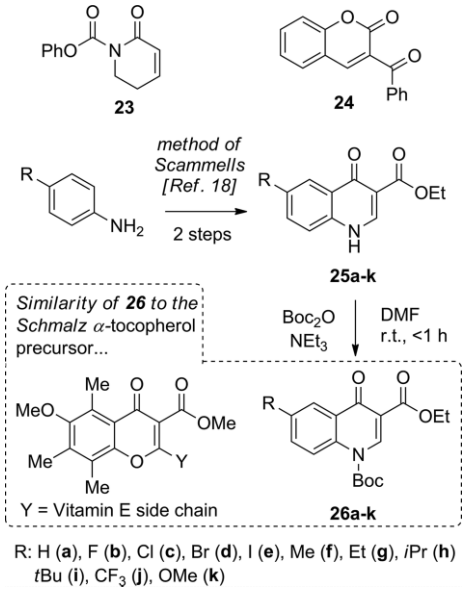
[a] Determined by $^1H$ NMR on the crude reaction mixture. [b] Isolated yield 80 %. [c] Isolated yield 99 %.

(10 mol-%) improved conversions are realised: $P(OPh)_3$ (88 %), $PPh_3$ (73 %) and $P(cC_6H_{11})_3$ (92 %). This indicates that any ligand accelerated catalysis[13] is modest and not strongly affected by the σ/ϖ-donor characteristics of the phosphine. In line with these observations screening of a small diverse library of chiral ligands (exemplars $\mathbf{L_A}$-$\mathbf{L_F}$)[10] produced at best 1–11 % *ee* at conversions of 21–76 %. The low levels of asymmetric induction realised are likely due to diverse substrate coordination shown by $Mg^{II}$ in 2-MeTHF.[14]

### Additions to Boc-Protected Ethyl 6-Substituted 4(1*H*)-Quinolone-3-carboxylates (26)

One way to overcome the issues raised by substrates **7** is to add additional coordinative groups to the acceptor to provide both greater control of the asymmetric transition state conformation and increase its reactivity allowing the use of more selective (more covalent) organometallics ($ZnR_2$, $AlR_3$). Substrates **23**[15]–**24**[16] (Scheme 3) represent examples of such approaches. We therefore initiated study of acceptors **26** which are attractive due to their similarity to Schmalz's asymmetric synthesis of Vitamin E (94 % *ee* for 1,4 $AlMe_3$ addition);[17] and as Scammells has described very short preparation of the parent precursor **25a**.

Synthesis of the acceptor library **26a**–**k** proceeded as expected,[10] but two points are worth noting: (i) the use of Eaton's reagent to cyclise the 6-substituted 4-oxo-1,4-dihydroquinolines **25** is much preferred over traditional phosphoric acids or high temperature cyclisations in $Ph_2O$ and we found this can be telescoped into a one-pot procedure; (ii) in Boc

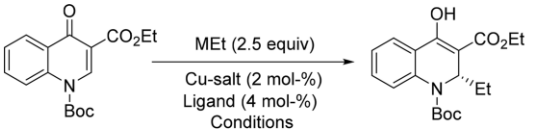



Scheme 3. Preferred heterocyclic motifs for improved selectivity in asymmetric additions and the synthesis of preferred acceptor **26**.[18]

protection of **25**, washing with $LiCl_{(aq)}$ to remove DMF avoids the degradation that even mildly acidic washes would cause.

Preliminary investigations focused of asymmetric catalytic studies on **26a** (Table 2). Previous studies had already revealed the ethyl ester is preferred over both smaller and larger groups (Me, $CHPh_2$) and that phosphoramidites are the optimal ligand class. The ligand structures used in the final optimisation are shown in Scheme 4.

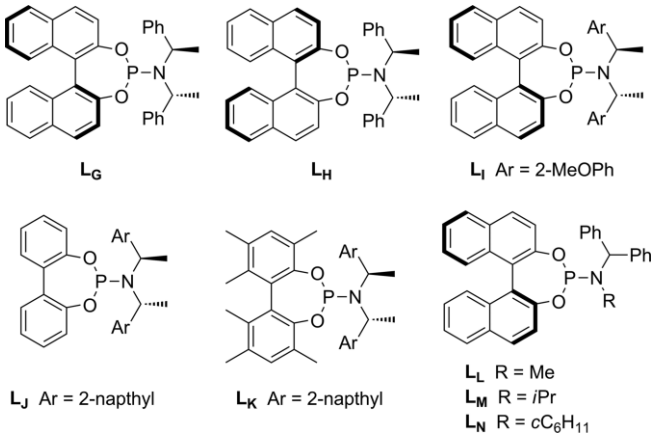
Table 2. Optimisation of $AlEt_3$ addition to Boc-protected 4(1*H*)-quinolone-3-carboxylate **26a**.




**26a** **27a**

| Run | MEt | Cu-source | Ligand | Solvent | Temp (°C) | Time (h) | Conv. (%)[a] | Ee (**27a**) |
|---|---|---|---|---|---|---|---|---|
| 1 | $AlEt_3$ | $Cu(OTf)_2$ | $\mathbf{L_G}$ | $CH_2Cl_2$ | -10 | <0.1 | >99 | <1 |
| 2 | $AlEt_3$ | $Cu(OTf)_2$ | $\mathbf{L_G}$ | THF | -10 | 0.5 | >99 | -18 |
| 3 | $AlEt_3$ | $Cu(OTf)_2$ | $\mathbf{L_G}$ | $Et_2O$ | -10 | 1 | >99 | 40 |
| 4 | $AlEt_3$ | $Cu(OTf)_2$ | $\mathbf{L_G}$ | $Et_2O$ | -25 | 1 | >99 | 60 |
| 5 | $AlEt_3$ | $Cu(OAc)_2$ | $\mathbf{L_G}$ | $Et_2O$ | -25 | 3 | 96 | 52 |
| 6 | $AlEt_3$ | $Cu(MeCN)_4BF_4$ | $\mathbf{L_G}$ | $Et_2O$ | -25 | 3 | 98 | 45 |
| 7 | $ZnEt_2$ | $Cu(OTf)_2$ | $\mathbf{L_G}$ | $Et_2O$ | -25 | <0.1 | >99 | 15 |
| 8 | $AlEt_3$ | $Cu(OTf)_2$ | $\mathbf{L_G}$ | $Et_2O$ | -40 | 6 | 98-99 | 65 |
| 9 | $AlEt_3$ | $Cu(OTf)_2$ | $\mathbf{L_G}$ | $Et_2O$ | -40 | 6-24 | >99[b] | 65 |
| 10 | $AlEt_3$ | $Cu(OTf)_2$ | $\mathbf{L_H}$ | $Et_2O$ | -40 | 24 | 22 | – |
| 11 | $AlEt_3$ | $Cu(OTf)_2$ | $\mathbf{L_I}$ | $Et_2O$ | -40 | 24 | 87 | 5 |
| 12 | $AlEt_3$ | $Cu(OTf)_2$ | $\mathbf{L_J}$ | $Et_2O$ | -40 | 24 | >99 | 12 |
| 13 | $AlEt_3$ | $Cu(OTf)_2$ | $\mathbf{L_K}$ | $Et_2O$ | -40 | 24 | >99 | 26 |
| 14 | $AlEt_3$ | $Cu(OTf)_2$ | $\mathbf{L_L}$ | $Et_2O$ | -40 | 24 | >99 | 2 |
| 15 | $AlEt_3$ | $Cu(OTf)_2$ | $\mathbf{L_M}$ | $Et_2O$ | -40 | 24 | >99 | 70 |
| 16 | $AlEt_3$ | $Cu(OTf)_2$ | $\mathbf{L_N}$ | $Et_2O$ | -40 | 24 | >99[c] | **77**[d] |

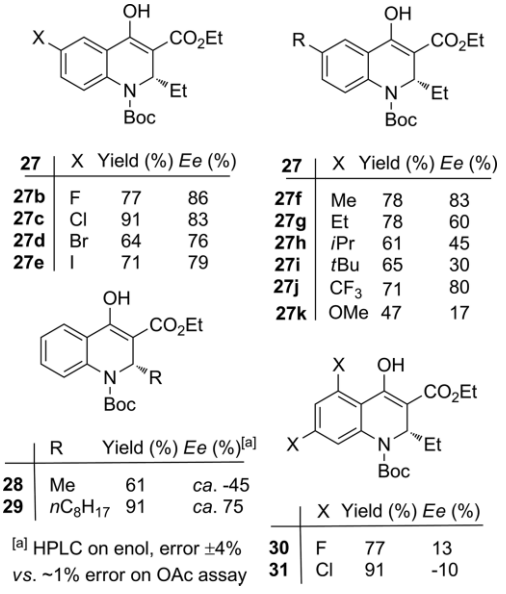
[a] Determined by $^1H$ NMR on the crude reaction mixture. [b] Isolated yield 68 %. [c] Isolated yield 73 %. [d] 77–82 % *ee* at 4 mol-% $Cu(OTf)_2$ and 8 mol-% $\mathbf{L_N}$.




Scheme 4. Ligands used for catalytic asymmetric additions of MR to acceptor **26a**.

Initial trials (Table 2) identified $Et_2O$ as an optimal solvent (Runs 1–3) and that copper(II) triflate was the optimal pre-catalyst for asymmetric $AlEt_3$ 1,4-addition (Runs 4–6) using (*S*,*R*,*R*) Feringa's ligand $\mathbf{L_G}$ as a starting phosphoramidite. Alternative additions of $ZnEt_2$ provided poorer performance (Run 7 is representative). For $AlEt_3$ additions cooling the reaction to –40 °C led to the highest *ee* value, but an increase in reaction time is required (Runs 8–9). We postulate that the success of the ether solvent is due to the relative insolubility of **26a** in it at low temperature which somewhat moderates background (uncatalysed) reactions. At –40 °C in the absence of any catalyst a 74 % conversion of **25a** is seen at 24 h. Lower temperatures could not be used to further moderate this, as all reactions (catalysed or background) shut down at –50 °C. We have seen similar effects before.[16] Ligand modification to include addition coordination ($\mathbf{L_I}$, Run 11), increase in steric bulk of both the amine ($\mathbf{L_J}$) or atropisomeric diol ($\mathbf{L_K}$) (Runs 12–13) had detrimental effects on the selectivity. The performance of the dissymmetric ligands ($\mathbf{L_L}$-$\mathbf{L_N}$) was maximised for a cyclohexyl substituent (Runs 14–16). Finally, as the reaction is close to viability at –40 °C we assured its reproducibility, performance and conversion by increasing the catalyst loadings to 4 mol-% $Cu(OTf)_2$ and 8 mol-% $\mathbf{L_N}$. Using these optimised conditions we investigated the effect of the 6-substituent on the catalytic reaction performance (Scheme 5).

The behaviour of **27a**–**k** indicate that electron withdrawing groups in the 6-position increase the stereoselectivity of $AlEt_3$ 1,4-addition. Steric demand in the 6-position has a detrimental effect on the selective transition state, but less so than electron factors. With respect to the alane, $AlMe_3$ reversed the sense of asymmetric induction (**28**), but longer linear alkyl chains were tolerated and behaved similarly to $AlEt_3$ (**29**). Disubstituted **30**–**31** are clearly not accepted by the reaction transition state, but the root cause of this issue is not apparent at present. Due to the apparent reversals of enantioselectivity (e.g. **27a** vs. **28**), based on sign of optical rotation and HPLC enantiomer elution order, it became important to identify the absolute sense of the asymmetric induction engendered by (*S*)-$\mathbf{L_N}$ in $AlEt_3$ addition to **26a**, and by implication other combinations of acceptors and alanes. Unfortunately, all of the direct conjugate addition products **27** we encountered were oils. However, we could overcome this issue and attain a crystalline derivative by manipulation of **27a** (Scheme 6).




| 27 | X | Yield (%) | *Ee* (%) |
|---|---|---|---|
| **27b** | F | 77 | 86 |
| **27c** | Cl | 91 | 83 |
| **27d** | Br | 64 | 76 |
| **27e** | I | 71 | 79 |

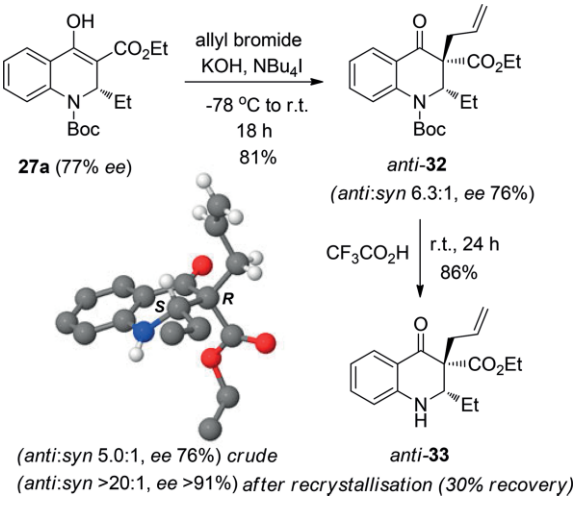
| 27 | X | Yield (%) | *Ee* (%) |
|---|---|---|---|
| **27f** | Me | 78 | 83 |
| **27g** | Et | 78 | 60 |
| **27h** | *i*Pr | 61 | 45 |
| **27i** | *t*Bu | 65 | 30 |
| **27j** | $CF_3$ | 71 | 80 |
| **27k** | OMe | 47 | 17 |

| | R | Yield (%) | *Ee* (%)[a] |
|---|---|---|---|
| **28** | Me | 61 | *ca.* -45 |
| **29** | $nC_8H_{17}$ | 91 | *ca.* 75 |

[a] HPLC on enol, error ±4% *vs.* ~1% error on OAc assay

| | X | Yield (%) | *Ee* (%) |
|---|---|---|---|
| **30** | F | 77 | 13 |
| **31** | Cl | 91 | -10 |

Scheme 5. Scope and limitations of substitution patterns for 4(1*H*)-quinolone-3-carboxylate acceptors.




Scheme 6. Stereo-correlation of (+)-**27a** to crystallographically characterised (*2S*,*3R*)-**33** via selective allylation, to *anti*-**32**, and Boc-deprotection. Only hydrogens on the allyl, amine and C2-methine groups of **33** are shown. Selected bond lengths: N1–C2 1.450(6), 1.439(6); C2–C3 1.555(6), 1.558(6); C3–C4 1.524(7), 1.543(7) Å and N1–C1–C2–C3 torsion angle: 43.4(5), 48.2(5). There are two independent molecules in the unit cell of **33** (CCDC 1967992).

A sample of 77 % *ee* (+)-**27a** was allylated under non-polar mild conditions leading to the formation of a major allyl *anti* diastereomer **32** with the same optical purity, within experimental error as the starting material. Deprotection of **32** with trifluoroacetic acid leads to formation of a similar mixture of stereoisomers, of which the *anti*-(**33**) species is significantly the most abundant. Fortunately, slow addition of pentane to concentrated ether solutions of the **33** mixture leads to the formation of modest crops of yellow needles of (+)-**33**, which by crys-

tallography are the single isomer *anti*-(+)-(2*S*,3*R*)-**33**.[10] Thus (+)-**27a** also has the 2*S* configuration presented throughout this paper. Based on the similarity of their chiral (Chiralpak AD-H) HPLC enantiomer elution and the homology of their polarimetry results we tentatively suggest that **27a**–**k** and **28**–**31** have the stereochemistry implied herein.

## Conclusions

While new 1,4-addition of *akyl* Grignard reagents to protected quinolin-4(1*H*)-ones (**7**) proceed efficiently (54–99 % yield) under CuBr•$SMe_2$/$PPh_3$ catalysis (5/10 mol-%) attempts to render the process asymmetric are not successful ($ee_{max} \approx 11$ %). However, modification of the quinolin-4(1*H*)-one core by addition of an ester directing/activating group at the 3-position allows asymmetric additions of $AlR_3$ (R = Me, Et, $nC_8H_{17}$) under Cu(OTf)$_2$/phosphoramidite (4/8 mol-%) catalysis. The best ligands are the dis-symmetric ligands introduced by Fletcher, especially (*S*)-$\mathbf{L_N}$.[19] Stereoselectivities in the range from: –45 to +86 % *ee* are observed, with the highest selectivities being associated with those 4(1*H*)-quinolone-3-carboxylate acceptors (**26**) bearing small electron withdrawing substituents at the 6-position. The sense of asymmetric induction, due to (*S*)-$\mathbf{L_N}$, could be determined by C3-allylation and subsequent *N*-deprotection to afford crystals of ethyl (2*S*,3*R*)-3-allyl-2-ethyl-2,3-dihydro-4(1*H*)-quinolone-3-carboxylate (2*S*,3*R*)-(**33**). As no general ligand providing > 90 % *ee* over a range of 4(1*H*)-quinolone-3-carboxylates was identified it is likely that individual substrate optimisation will be required. Rather than *ad hoc* screening we propose *in silico* ligand screening of a test transition state, modelled out of our own mechanistic studies,[20] but using the substrates employed here may be an attractive alternative strategy to the discovery of such systems. Such investigations are our next target.

## Experimental Section

**General:** Details of our general laboratory set-up and instrumentation have been already published.[21] In brief, 2-Me-THF and $Et_2O$ were distilled from sodium-benzophenone. For catalytic procedures Grignard and alane reagents and copper salts were commercial products. Ligands and starting materials were prepared by literature procedures.[10] Further details for the processes and compounds described in this paper are within the Supporting Information.

**Optimised General Procedure for Conjugate Addition of Grignard Reagents to Acceptors 7** (Table 1 and Scheme 2)**:** To a solution of the protected quinolone substrate (**7b**–**d**, 1 equiv.) in 2-methyl tetrahydrofuran (0.2 M solution), copper bromide dimethyl sulfide complex (0.05 equiv.) and triphenylphosphine (0.1 equiv.) were added with stirring at –78 °C. Under an argon atmosphere was added a solution of the Grignard reagent (2.5 equiv.). The reaction mixture was stirred at –78 °C under an argon atmosphere for 1 hour. Water (0.1 mL per mmol of **7b**–**d**) was added to the reaction mixture which was warmed to r.t. whilst stirring over 10 minutes. The reaction mixture was partitioned between $Et_2O$ and water and the phases separated. The aqueous phase was re-extracted with $Et_2O$ (3 × 10 mL). The combined organic phases were washed with water (15 mL), dried ($MgSO_4$), concentrated in vacuo and purified by column chromatography (silica, 9:1 pentane/$Et_2O$) to afford the products **8b**–**d** as described. The catalytic trials of Table 1 were performed in a similar manner but at 0.1–0.3 mmol scales with estimations of the conversions made by $^1$H NMR spectroscopy prior to chromatography (runs 8–9 only).

**Benzyl 2-Ethyl-4(1*H*)-quinolone-1-carboxylate (8b):** The general procedure was followed with compound **7b** (903 mg, 3.23 mmol) and ethylmagnesium bromide (3.0 M in THF) (2.7 mL, 8.1 mmol) to afford compound **8b** as a colourless solid (798 mg, 2.58 mmol, 80 %); m.p. 74–76 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 8.00 (dd, *J* = 7.8, 1.7 Hz, 1 H, , $C^5$H), 7.81 (d, *J* = 8.2 Hz, 1H, $C^8$H), 7.54 (ddd, *J* = 8.2, 7.8, 1.7 Hz, 1H), 7.46–7.33 (m, 5H, 2 × $C^{12}$H, 2 × $C^{13}$H, $C^{14}$H), 7.19 (dd, *J* = 7.8 Hz, 7.8 Hz, 1H, $C^6$H), 5.32 (s, 2H, $C^{10}H_2$), 4.94 (dtd, *J* = 9.9, 5.8, 1.7 Hz, 1H, $C^2$H), 3.07 (dd, *J* = 17.6, 5.8 Hz, 1H, $C^3H_AH_B$), 2.67 (dd, *J* = 17.6, 1.8 Hz, 1H, $C^3H_AH_B$), 1.73–1.38 (m, 2H, $C^{15}H_2$), 0.90 (t, *J* = 7.4 Hz, 3H, $C^{16}H_3$); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) $\delta_C$ = 193.4 (C), 154.2 (C), 140.9 (C), 135.8 (C), 134.4 (C), 128.7 (CH), 128.4 (CH), 128.1 (CH), 126.8 (CH), 125.0 (CH), 124.7 (CH), 124.2 (CH), 68.2 ($CH_2$), 55.4 (CH), 43.2 ($CH_2$), 24.6 ($CH_2$), 10.7 ($CH_3$); IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3051, 2968, 1685 (C=O), 1602, 1481, 1461, 1395, 1341, 1323, 1304, 1272, 1240, 1127, 909; HRMS *m/z* calcd. for $C_{19}H_{20}NO_3$ [M + H]: 310.1438, found 310.1451 (σ = 3.70 ppm). An alternative method to **8b** has appeared, but no data were presented.[10]

***tert*-Butyl 2-Ethyl-4(1*H*)-quinolone-1-carboxylate (8c):** The general procedure was followed with compound **7c** (245 mg, 1.00 mmol) and ethylmagnesium bromide (3.0 M solution in THF) (0.85 mL, 2.55 mmol) to afford compound **8c** as a colourless solid (273 mg, 0.991 mmol, 99 %); m.p. 65–66 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.98 (dd, *J* = 7.8, 1.6 Hz, 1H, $C^5$H), 7.79 (app. d, *J* = 8.6 Hz, 1H, $C^8$H), 7.52 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H, $C^7$H), 7.15 (dd, *J* = 7.8, 7.3 Hz, 1H, $C^6$H), 4.85 (app. dtd, *J* = 7.3, 5.8, 1.6 Hz, 1H, $C^2$H), 3.06 (dd, *J* = 17.5, 5.8 Hz, 1H, $C^3H_AH_B$), 2.65 (dd, *J* = 17.5, 1.7 Hz, 1H, $C^3H_AH_B$), 1.79–1.37 (m, 11H, 3 × $C^{11}H_3$, $C^{12}H_2$), 0.91 (t, *J* = 7.3 Hz, 3H, $C^{13}H_3$); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) $\delta_C$ = 193.8 (C), 153.3 (C), 141.5 (C), 134.1 (C, CH), 126.7 (CH), 124.8 (CH), 123.6 (CH), 82.0 (C), 55.0 (CH), 43.2 ($CH_2$), 28.3 ($CH_3$), 24.7 ($CH_2$), 10.7 ($CH_3$); IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3078, 3011, 2976, 2934, 2879, 1683 (C=O), 1601, 1576, 1480, 1461, 1370, 1348, 1304, 1284, 1256, 1163, 1127, 1066, 1047, 1025, 1003; HRMS *m/z* calcd. for $C_{16}H_{21}NNaO_3$ [M + Na]: 298.1404, found 298.1407 (σ = 1.40 ppm). An alternative method to **8c** has appeared, but no data were presented.[10]

**Methyl 2-Ethyl-4(1*H*)-quinolone-1-carboxylate (8d):** The general procedure was followed with compound **7d** (88 mg, 0.43 mmol) and ethylmagnesium bromide (3.0 M in THF) (0.35 mL, 1.05 mmol) to afford compound **8d** as a colourless oil (79 mg, 0.339 mmol, 79 %); m.p. 74–76 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.99 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.58–7.51 (m, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 4.94–4.86 (m, 1H, $C^2$H), 3.87 (s, 3H, $C^{10}H_3$), 3.06 (dd, *J* = 17.6, 5.8 Hz, 1H, $C^3H_AH_B$), 2.66 (dd, *J* = 17.6, 1.0 Hz, 1H, $C^3H_AH_B$), 1.68–1.43 (m, 1H, $C^{11}H_AH_B$), 1.22 (app. t, *J* = 7.2 Hz, 1H, $C^{11}H_AH_B$), 0.90 (app. t, *J* = 7.2 Hz, 3H); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) $\delta_C$ = 193.5 (C), 154.9 (C), 140.9 (C), 134.4 (C), 126.8 (CH), 125.0 (CH), 124.7 (CH), 124.2 (CH), 55.4 (CH), 53.3 ($CH_3$), 43.1 ($CH_2$), 24.6 ($CH_2$), 10.7 ($CH_3$); IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3011, 2972, 1684, 1603, 1481. 1461, 1442, 1389, 1348, 1304, 1282, 1193; HRMS *m/z calcd.* for $C_{13}H_{16}NO_3$ [M + H]: 234.1125, found 234.1120 (σ = 2.20 ppm).

**Representative Procedure for $AlR_3$ Conjugate Addition Product (*S*)-27 and Their Subsequent acetylation** (Table 2 and Scheme 5)**:** A suspension of protected quinolone derivative (1 equiv.), Cu(OTf)$_2$ (2 or 4 mol-%; 2 or 4 for **26a**, 4 for all other **26**) and ligand (typically $\mathbf{L_N}$ 4 or 8 mol-%; 2 or 4 for **26a**, 4 for all other **26**) in freshly distilled anhydrous $Et_2O$ (0.1 M in acceptor **25**) was stirred under an argon

atmosphere at r.t. for 30 minutes. The suspension was then cooled to –40 °C and stirred at this temperature under an argon atmosphere for a further 15 minutes. To the suspension was added $AlEt_3$ (1.3 M solution in heptane) (2.5 equiv.) via dropwise addition allowing the organometallic solution to cool prior to contact with the suspension by running down the side of the reaction vessel. The reaction mixture was stirred under an atmosphere of argon at –40 °C until completion (see specified times). A saturated solution of potassium sodium tartrate was then added to the reaction mixture and warmed to r.t. whilst stirring over 30 minutes. The reaction mixture was partitioned between $CH_2Cl_2$ and water and the phases were separated. The aqueous phase was extracted with $CH_2Cl_2$ (3 times). The combined organics were washed with water (once), dried ($MgSO_4$), concentrated in vacuo and purified either by column chromatography (silica, 97:3 pentane/$Et_2O$) or preparative thin layer chromatography (silica, $CH_2Cl_2$) to afford the conjugate addition products **27** as described. The preparation of **28**–**29** was attained in an equivalent manner. Enol tautomers dominate (enol:keto 95:5–80:20). Only signals relating to enol form are reported. Exchange of the products with minor keto tautomers can cause signal broadening in chiral HPLC assays and higher error bars (±4 vs. ≈ 1 % *ee* error for acetate assay).

**Conversion of Scalemic (*S*)-27 Into Derived Acetates**: The conjugate addition product was dissolved in 1:1 mixture of $Ac_2O$/pyridine (0.5 M solution) and stirred at r.t. for 24 h. Isolated acetate products were confirmed by $^1H$ NMR spectroscopy. HPLC chromatograms were obtained on small amounts of acetylated material isolated via thin layer chromatography on the remainder of the products.

**1-*tert*-Butyl 3-Ethyl (*S*)-2-Ethyl-4-hydroxy-1,2-dihydroquinoline-1,3-dicarboxylate (27a):** The general procedure was followed using the protected quinolone carboxylate **26a** (2.54 g, 8.00 mmol) and triethylaluminium (1.3 M in heptane) (15.5 mL, 20.2 mmol, 24 h) to afford compound **27a** as a colourless oil (2.03 g, 5.84 mmol, 73 %); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 12.12 (s, 1H, OH), 7.78 (dd, *J* = 7.7, 1.6 Hz, 1H, $C^5H$), 7.63 (br s, 1H, $C^8H$), 7.40 (ddd, *J* = 8.4, 7.4, 1.6 Hz, 1H, $C^7H$), 7.17 (ddd, *J* = 7.7, 7.4, 1.1 Hz, 1H, $C^6H$), 5.39 (dd, *J* = 9.7, 4.9 Hz, 1H, $C^2H$), 4.42–4.25 (m, 2H, $C^{15}H_2$), 1.55 (s, 9H, 3 × $C^{11}H_3$) overlapped by 1.56–1.45 (m, 1H, $C^{12}H_AH_B$), 1.38 (t, *J* = 7.1 Hz, 3H, $C^{16}H_3$) overlapped by 1.42–1.34 (m, 1H, $C^{12}H_AH_B$), 0.87 (t, *J* = 7.4 Hz, 3H, $C^{13}H_3$); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_C$ = 170.5 (C), 162.3 (C), 152.9 (C), 137.9 (C), 130.7 (CH), 125.0 (CH), 124.2 (CH), 123.8 (CH), 123.1 (C), 100.7 (C), 81.4 (C), 60.8 ($CH_2$), 51.9 (CH), 28.3 ($CH_3$), 26.7 ($CH_2$), 14.3 ($CH_3$), 10.3 ($CH_3$); IR (ATR): $\tilde{\nu}_{max}$ = 3488, 2977, 2933, 2875, 1702 (C=O), 1651, 1624, 1569, 1488, 1457, 1403, 1368, 1350, 1328, 1280, 1252, 1232, 1145, 1094, 1074, 1023, 904, 818, 766, 675, 521, 457; HRMS *m/z* calcd. for $C_{19}H_{25}NNaO_5$ [M + Na]: 370.1625, found 370.1625 (σ = 0.10 ppm); HPLC Keto–enol tautomerism led to broad signals in the chromatograms and increased error bars. Accurate *ee* measurement was attained on the derived acetate (See below for data). Chiralpak AD-H; mobile phase: hexane:2-propanol (99:1 v/v); flow rate: 0.8 mL $min^{-1}$; retention times: major enantiomer: 5.3 min (91.2 %), minor enantiomer: 14.2 min (8.8 %), 82 % *ee*; $[\alpha]_D^{20}$ = +256.3 (*c* = 1.0 in $CHCl_3$, 82 % *ee*).

**1-*tert*-Butyl 3-Ethyl (*S*)-4-Acetoxy-2-ethyl-1,2-dihydroquinoline-1,3-dicarboxylate (27a derived acetate):** The general procedure was followed using the conjugate addition product **26a** (278 mg, 0.800 mmol) to afford the derived acetate as a pale yellow oil (229 mg, 0.588 mmol, 74 %); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.71 (br s, 1H, $C^8H$), 7.42–7.32 (m, 2H), 7.13 (ddd, *J* = 8.2, 7.4, 1.1 Hz, 1H, $C^6H$), 5.56 (dd, *J* = 10.0, 4.4 Hz, 1H, $C^2H$), 4.33–4.21 (m, 2H, $C^{15}H_2$), 2.39 (s, 3H, $C^{18}H_3$), 1.68–1.59 (m, 1H, $C^{12}H_AH_B$) overlapped by water peak, 1.56 (s, 9H, 3 × $C^{11}H_3$), 1.47 (dtd, *J* = 14.1, 7.2, 2.7 Hz, 1H, $C^{12}H_AH_B$), 1.35 (t, *J* = 7.1 Hz, 3H, $C^{16}H_3$), 0.89 (t, *J* = 7.4 Hz, 3H, $C^{13}H_3$); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_C$ = 168.0 (C), 163.4 (C), 152.7 (C), 149.2 (C), 137.2 (C), 130.5 (CH), 124.8 (CH), 123.8 (CH), 123.6 (CH), 123.4 (C), 118.1 (C), 81.7 (C), 60.8 ($CH_2$), 53.8 (CH), 28.3 ($CH_3$), 25.5 ($CH_2$), 20.9 ($CH_3$), 14.2 ($CH_3$), 10.0 ($CH_3$); IR (ATR): $\tilde{\nu}_{max}$ = 2974, 2933, 2875, 1773 (C=O), 1700 (C=O), 1635, 1602, 1572, 1485, 1456, 1368, 1329, 1249, 1223, 1184, 1156, 1133, 1106, 1069, 1020, 1005, 904, 887, 870, 855, 759, 732, 646, 584, 521, 459, 433; HRMS *m/z* calcd. for $C_{21}H_{27}NNaO_6$ [M + Na]: 412.1731, found 412.1732 (σ = 0.40 ppm); HPLC Chiralpak AD-H; mobile phase: hexane:2-propanol (95:5 v/v); flow rate: 0.5 mL $min^{-1}$; retention times: major enantiomer: 10.1 min (88.5 %), minor enantiomer: 13.0 min (11.5 %), 77 % *ee*; $[\alpha]_D^{20}$ = +295.5 (*c* = 1.0 in $CHCl_3$, 77 % *ee*).

**1-*tert*-Butyl 3-Ethyl (2*S*,3*R*)-3-Allyl-2-ethyl-2,3-dihydro-4(1*H*)-quinolone-1,3-dicarboxylate (32):** To a stirred solution of compound **(+)-27a** (224 mg, 0.645 mmol, assayed as 77 % *ee*) in $CH_2Cl_2$ (4.3 mL, 0.15 M solution) at –78 °C was added potassium hydroxide (145 mg, 2.58 mmol), tetrabutylammonium iodide (24 mg, 0.065 mmol) and allyl bromide (112 μL, 1.29 mmol). The reaction vessel was shielded from light to prevent decomposition of the tetrabutylammonium iodide and the suspension was warmed slowly to r.t. whilst stirring over 18 h. The reaction mixture was partitioned between $CH_2Cl_2$ (10 mL) and $H_2O$ (5 mL). The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), concentrated in vacuo and purified by column chromatography (silica, $CH_2Cl_2$) to afford a mixture of four stereoisomers (≈ 3:10:76:10), of which *anti* (2*S*,3*R*)-**32** was the major component, as a colourless oil (203 mg, 0.524 mmol, 81 %); *anti*/*syn* ratio = 6.3:1 (only data for the major diastereomer are reported). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta_H$ = 8.05 (dd, *J* = 7.9, 1.7 Hz, 1H, $C^5H$), 7.79 (br d, *J* = 8.4 Hz, 1H, $C^8H$), 7.55 (ddd, *J* = 8.4, 7.2, 1.7 Hz, 1H, $C^7H$), 7.19 (ddd, *J* = 7.9, 7.2, 1.1 Hz, 1H, $C^6H$), 5.77 (dddd, *J* = 17.3, 10.2, 7.3, 7.0 Hz, 1H, $C^{18}H$), 5.12–5.03 (m, 2H, $C^{19}H_2$), 4.85 (dd, *J* = 10.7, 4.8 Hz, 1H, $C^2H$), 4.32–4.23 (2 × q, *J* = 7.1 Hz, 2H, $C^{15}H_2$), 2.88 (dddd, *J* = 14.2, 7.0, 1.3, 1.3 Hz, 1H, $C^{17}H_AH_B$), 2.60 (dddd, *J* = 14.2, 7.3, 1.2, 1.2 Hz, 1H, $C^{17}H_AH_B$), 1.59 (s, 9H, 3 × $C^{11}H_3$) overlapped by 1.61–1.52 (m, 2H, $C^{12}H_2$), 1.33 (t, *J* = 7.1 Hz, 3H, $C^{16}H_3$), 0.88 (t, *J* = 7.3 Hz, 3H, $C^{13}H_3$); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_C$ = 190.0 (C), 169.4 (C), 153.6 (C), 139.9 (C), 134.2 (CH), 131.8 (CH), 127.9 (CH), 124.4 (CH), 124.3 (C), 124.0 (CH), 119.3 ($CH_2$), 82.4 (C), 63.0 (C), 61.4 ($CH_2$), 61.2 (CH), 38.7 ($CH_2$), 28.3 ($CH_3$), 22.3 ($CH_2$), 14.1 ($CH_3$), 10.6 ($CH_3$); IR (ATR): $\tilde{\nu}_{max}$ = 3078, 2976, 2935, 2877, 1689 (C=O), 1600, 1479, 1459, 1367, 1332, 1253, 1218, 1154, 1127, 1078, 1013, 991, 923, 886, 758, 643, 582, 451; HRMS *m/z* calcd. for $C_{22}H_{30}NO_5$ [M + H]: 388.2118, found 388.2120 (σ = 0.30 ppm); HPLC Chiralpak AD-H; mobile phase: hexane/2-propanol (99:1 v/v); flow rate: 0.5 mL $min^{-1}$; retention times: major product (2*S*,3*R*)-**32**: 26.9 min (76.1 %), 76 % *ee*; minor *syn*-allylation product (2*S*,3*S*)-**32**: 31.1 min (10.3 %), enantiomer of major product (2*R*,3*S*)-**32**: 20.0 min (10.3 %), enantiomer of minor *syn*-allylation product (2*R*,3*R*)-**32**: 10.8 min (3.4 %). The *ee* value of the minor *syn* diastereomer of **32** could not be accurately determined due to peak overlap, measured at ≥ 50 % *ee*; $[\alpha]_D^{20}$ = +68.0 (*c* = 1.0 in $CHCl_3$, for a ≈ 3:10:76:10 mixture of the 2*R*,3*R*/2*R*,3*S*/2*S*,3*R*/2*S*,3*S* isomers).

**Ethyl (2*S*,3*R*)-3-Allyl-2-ethyl-2,3-dihydro-4(1*H*)-quinolone-3-carboxylate (33):** To a stirring solution of the mixture of stereoisomers **32** (310 mg, 0.80 mmol) in $CH_2Cl_2$ (2.4 mL, 0.33 M solution) at r.t. was added trifluoroacetic acid (1.6 mL). The solution was stirred at r.t. for 24 h then diluted with $CH_2Cl_2$ (9.6 mL) and added slowly to a saturated aqueous solution of $NaHCO_3$ (12 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3 × 12 mL). The combined organics were washed with $H_2O$ (24 mL), dried ($MgSO_4$), concentrated in vacuo and purified by column chromatography (silica, $CH_2Cl_2$) to

afford **33** as a bright yellow solid (198 mg, 0.689 mmol, 86 %; as a mixture of four stereoisomers ≈ 14:3:73:10). The major species was assigned to *anti* (2*S*,3*R*)-**33**. The mixture was recrystallised from ≈ 5:1 pentane/$Et_2O$ at r.t. to afford stereo enriched (2*S*,3*R*)-**33** as bright yellow needles (≈ 30 % yield, > 91 % *ee*, > 90:1 *dr* by HPLC, > 20:1 by NMR); X-ray crystallographic analysis confirmed the 2*S*,3*R* stereochemistry of the major stereoisomer; NMR data for only major 2*S*,3*R* isomer. M.p. 83–85 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ = 7.94 (dd, *J* = 8.0, 1.6 Hz, 1H, $C^5H$), 7.33 (ddd, *J* = 8.2, 7.1, 1.6 Hz, 1H, $C^7H$), 6.80 (td, *J* = 8.0, 7.1, 1.0 Hz, 1H, $C^6H$), 6.70 (dd, *J* = 8.2, 1.0 Hz, 1H, $C^8H$), 5.74 (dddd, *J* = 17.1, 10.2, 9.2, 5.4 Hz, 1H, $C^{15}H$), 5.19 (ddd, *J* = 17.1, 1.7, 0.9 Hz, 1H, $C^{16}H_AH_B$), 5.11 (ddd, *J* = 10.2, 1.7, 0.9 Hz, 1H, $C^{16}H_AH_B$), 4.37 (s, 1H, NH), 4.14 (dq, *J* = 10.8, 7.1 Hz, 1H, $C^{12}H_AH_B$), 4.05 (dq, *J* = 10.8, 7.1 Hz, 1H, $C^{12}H_AH_B$), 3.47 (dd, *J* = 10.6, 2.3 Hz, 1H, $C^2H$), 3.19 (ddt, *J* = 14.2, 5.5, 1.7 Hz, 1H, $C^{14}H_AH_B$), 2.66 (dd, *J* = 14.2, 9.2 Hz, 1H, $C^{14}H_AH_B$), 2.01 (ddd, *J* = 14.4, 7.5, 2.3 Hz, 1H, $C^9H_AH_B$), 1.78 (ddd, *J* = 14.4, 10.6, 7.5 Hz, 1H, $C^9H_AH_B$), 1.10 (t, *J* = 7.1 Hz, 3H, $C^{13}H_3$), 1.07 (t, *J* = 7.5 Hz, 3H, $C^{10}H_3$); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): $\delta_C$ = 191.0 (C), 170.2 (C), 150.4 (C), 134.8 (CH), 133.1 (CH), 128.4 (CH), 119.8 (C), 118.9 ($CH_2$), 118.3 (CH), 115.5 (CH), 61.1 ($CH_2$), 60.0 (C), 59.6 (CH), 34.5 ($CH_2$), 21.6 ($CH_2$), 13.9 ($CH_3$), 11.2 ($CH_3$); IR (ATR): $\tilde{\nu}_{max}$ = 3370, 3075, 2978, 2927, 1727 (C=O), 1661, 1638, 1608, 1505, 1484, 1464, 1435, 1388, 1344, 1307, 1258, 1222, 1203, 1158, 1111, 1093, 1048, 1031, 994, 921, 860, 781, 754, 650, 621, 529, 491, 444; HRMS *m/z* calcd. for $C_{17}H_{22}NO_3$ [M + H]: 288.1594, found 288.1599 (σ = 1.80 ppm); **HPLC** (before crystallisation) on Chiralpak AD-H; mobile phase: hexane:2-propanol (99:1 v/v); flow rate: 0.5 mL min$^{-1}$; retention times for purified sample: major product *anti* (2*S*,3*R*)-**33-**24.7 min (73.1 %), 76 % *ee*; minor *anti* enantiomer (2*R*,2*S*)-**33-**28.3 min (10.0 %), minor *syn*-allylation product (2*S*,3*S*)-**33-**18.2 min (3.2 %), 66 % *ee*, enantiomer of *syn* product (2*R*,3*S*)-**175-**20.6 min (13.6 %); *anti*/*syn* ratio = 5.0:1 by HPLC. After recrystallisation the bulk sample showed *anti* (2*S*,3*R*)-**33** with > 91 % *ee* and > 90:1 vs. all other diastereomers from which the X-ray crystal was selected.[S29] $[\alpha]_D^{20}$ = +14.4, purified sample (after chromatography (*c* = 1.0 in $CHCl_3$, for a ≈ 14:3:73:10 mixture of the 2*S*,3*S*/2*R*,3*R*/2*S*,3*R*/2*R*,3*S* isomers); recrystallised sample: +24.0 (*c* = 1.0 in $CHCl_3$, > 91 % *ee*, > 90:1 *dr*).

CCDC 1967992 (for **33**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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**Keywords:** Alanes · Copper · Asymmetric catalysis · Michael addition · Phosphane ligands

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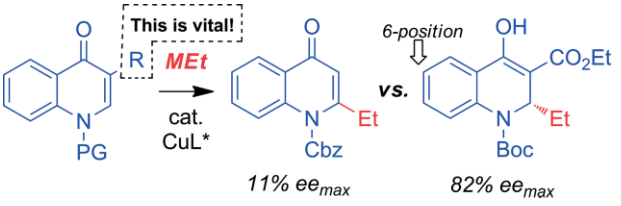
**Copper-Catalyzed 1,4-Addition**






Directing ester functions (R = $CO_2Et$) "give a big hand" to copper catalysed 1,4-additions of organometallics to medicinally relevant quinolin-4(1*H*)-ones. In the absence of any directing group only 11 % *ee* is realised for the addition of EtMgBr. In the presence of the $CO_2Et$ activating group, $AlEt_3$ may be added in up to 82 % *ee* providing 6-halo building block starting materials for quinolone species.

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