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The first enantioselective vinylogous Mukaiyama-type dearomatisation of heteroarenes under anion-binding catalysis is presented. A recyclable tetrakistriazole catalyst was used for the enantiocontrol of the remote vinylogous active position of silyl dienol ethers. This approach provided chiral heterocycles bearing α,β -unsaturated chains with complete regioselectivity and excellent enantioselectivities (up to 97.5:2.5 e.r.).

Asymmetric vinylogous-Mukaiyama reactions have become a powerful tool for the generation of multifunctional chiral scaffolds commonly occurring in natural products bearing easily derivatisable unsaturated carbon chains, which allow the construction of more complex structures.¹ Based on Fuson's principle of vinylogy,² the incorporation of an additional adjacent double bond to silyl enol ethers extends and strengthens their nucleophilicity at the γ -position, which provides a different, appealing connectivity in the products. As a result, several enantioselective approaches for vinylogous Mukaiyama-type reactions have been developed with silyl dienolates.¹ Among them, multiple organocatalytic systems based on different activation modes, including hydrogen-bonding, Lewis-base and ion-pairing catalysis, have been described (eqn (A), Scheme 1).³ However, vinylogous Mukaiyama reactions under anion-binding organocatalysis⁴ has long been prevented, most probably as a consequence of the long-range enantioinduction that the silyl dienolate would require.⁵

Enantioselective vinylogous-Mukaiyama-type dearomatisation by anion-binding catalysis[†]

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Inspired by the power of dearomatisation methods⁶ and the anion-binding catalysed asymmetric functionalisation of activated N-heteroarenes such as (iso)quinolines and pyridines by nucleophilic addition,^{4,7,8} we tackled this deficiency in the vinylogous-Mukaiyama technology. To the best of our knowledge, the use of silyl dienol ether derivatives as vinylogous nucleophiles in this type of asymmetric dearomatisation process has never been accomplished. This approach will allow straightforward access to highly functionalised enantiopure N-heterocyclic derivatives, which are abundant structural motifs in high demand for drug discovery processes,^{9–11} in a single operation from readily available heteroaromatic platforms.¹²

Based on previous studies,^{8d,13} we envisioned that multideterminate foldameric triazole-based catalysts, able to form a chiral contact ion-pair by recognition of the counterion of the *in situ* generated *N*-acyl salt as well as bridge both the cationic substrate and nucleophile, would be an excellent platform to test this vinylogous reaction. Hence, in this work, we present the asymmetric dearomatisation of heteroarenes such as quinazolines with silyl dienol ethers, enabling the first vinylogous

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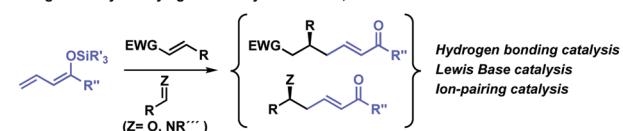
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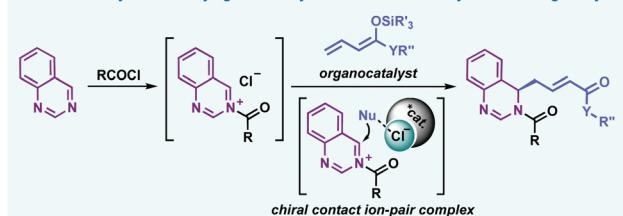
[†] Electronic supplementary information (ESI) available: Synthetic procedures, analytical data of new compounds, SFC and HPLC chromatograms, kinetics, X-ray analysis of 4k and NMR collection (PDF). CCDC 2069596. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc03514b

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A. Organocatalytic vinylogous-Mukaiyama Michael, Aldol & Mannich reactions



B. This work. Asymmetric vinylogous-Mukaiyama-dearomatization by anion-binding catalysis



Scheme 1 Previous organocatalytic vinylogous Mukaiyama strategies (eqn (A)) and the present work (eqn (B)).



Mukaiyama, Mannich-type dearomatization reaction under anion-binding catalysis (eqn (B), Scheme 1).

We began our investigations by studying the reaction of quinazoline (**2a**) as the model substrate with *tert*-butyldimethylsilyl (TBS)-substituted methylcrotonate nucleophile **3a** (Table 1, see the ESI† for full screening). The reaction was performed in the presence of different hydrogen-bond (HB) donor organocatalysts **1** and 2,2,2-trichloroethoxycarbonyl chloride (TrocCl) as the acylating agent for the *in situ* formation of the quinazolinium salt. At first, all catalysts were examined in MTBE at -78°C (entries 1–5), as a strong uncatalysed background reaction to form a regioisomeric mixture of the vinylogous products **4a** and **4a'** was always observed (1.7:1 ratio, entry 6).¹⁴ Interestingly, catalytic reactions with the HB-donors **1** only delivered the C4-addition product **4a**. The tetrakistriazoles **1a** and **1b** showed superior efficiency regarding both yield and enantioselectivity (entries 1 and 2), while the more powerful HB-donor bis thiourea **1e** displayed almost no stereocontrol (entry 5). After selecting **1a** as the optimal catalyst, the catalytic loading was considered (entries 7 and 8), the best enantioselectivity was shown when employing 3 mol% of **1a** (entry 7). Finally, changing the solvent to toluene led to the 3,4-dihydroquinazoline **4a** in an enhanced excellent enantioselectivity of 95.5:4.5 e.r. (entry 10).

Table 1 Optimisation of the Mukaiyama-dearomatisation^a

Entry	Cat. (mol%)	Solvent	4a/4a' ^b	Yield 4a ^c (%)	e.r. ^d
1	1a (10)	MTBE	>25:1	69	84:16
2	1b (10)	MTBE	>25:1	69	82:18
3	1c (10)	MTBE	>25:1	46	77:23
4	1d (10)	MTBE	>25:1	58	75:25
5	1e (10)	MTBE	>25:1	48	52:48
6	—	MTBE	1.7:1	49 ^e	—
7	1a (3)	MTBE	>25:1	73	90:10
8	1a (1)	MTBE	>25:1	63	88:12
9	1a (3)	Et ₂ O	>25:1	54	87:13
10	1a (3)	Toluene	>25:1	57	95.5:4.5

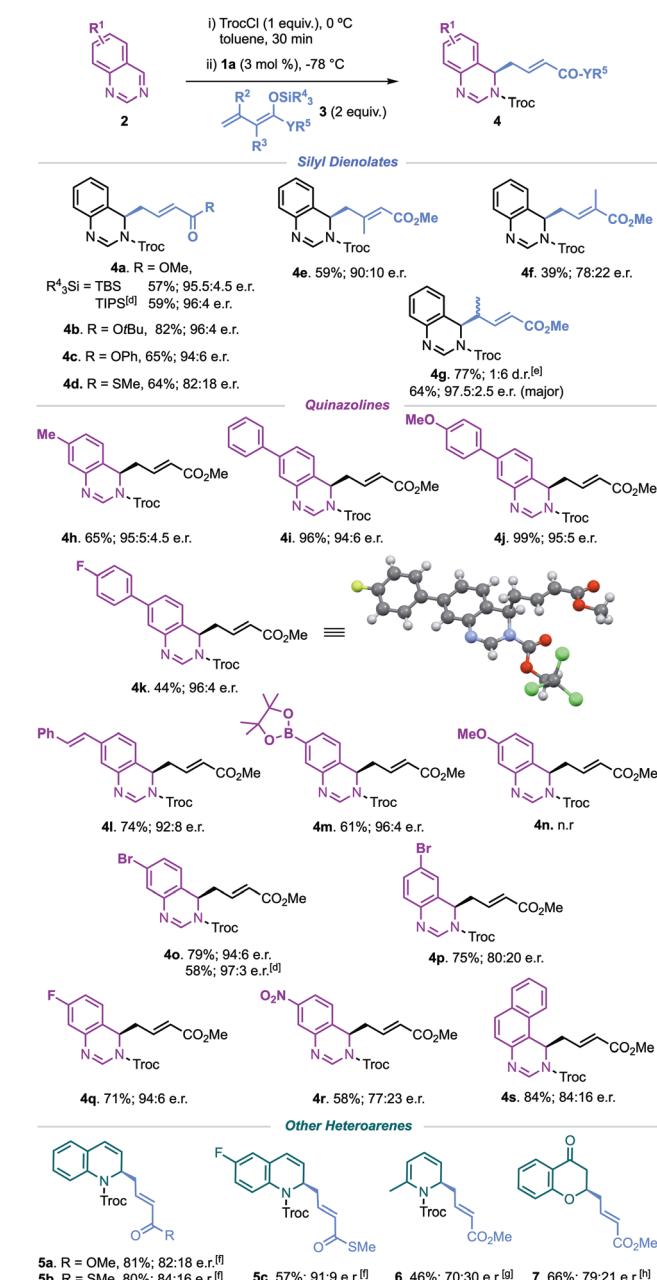
^a Conditions: (i) **2a** (0.1 mmol, 1 equiv.) and TrocCl (1 equiv.) in the appropriate solvent at 0°C , 30 min; (ii) at -78°C , catalyst **1** (x mol%) and **3a** (2 equiv.) were added and the reaction was stirred for 18 h.

^b **4a/4a'** ratio determined using ¹H NMR of the reaction mixture. ^c Yield of the isolated product.

^d The enantiomeric ratios (e.r.) were measured using chiral-phase SFC. ^e In the uncatalysed reaction, **4a** was formed in 31% yield and the C2-addition regioisomer **4a'** in 18% yield (see the ESI).

With the optimised conditions in hand (entry 10, Table 1), the scope of the reaction was studied (Table 2). Different silyldienol derivatives were initially tested (Table 2, top). While the *tert*-butyl and phenyl dienol ethers performed very efficiently, giving rise to the desired products (**4b** and **4c**) in excellent

Table 2 Scope of the enantioselective Mukaiyama-type reaction^{a–c}



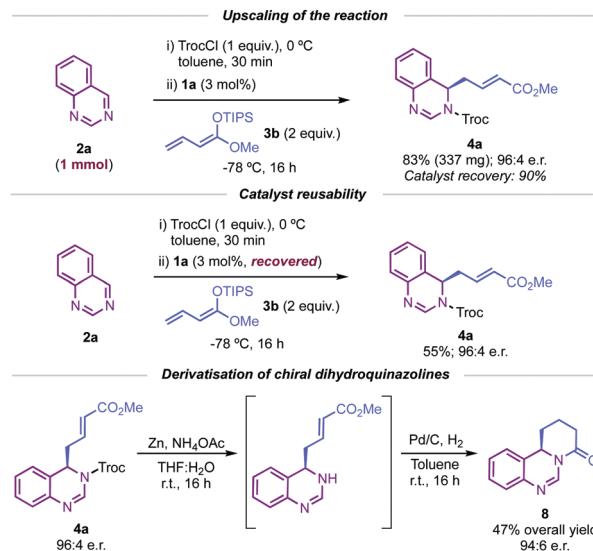
^a Reaction conditions: (i) **2** (0.1 mmol, 1.0 equiv.) and TrocCl (1.0 equiv.) in toluene 30 min at 0°C ; (ii) after cooling down to -78°C , **1a** (3 mol%) and TBS-3 (2 equiv.) were added and the reaction was stirred for 18–24 h. ^b Yields of the isolated products. ^c Enantioselective ratios determined using chiral-phase SFC. ^d Reaction performed with TIPS-dienolate **3b**. ^e Determined using ¹H NMR. ^f Reaction using **1d** (10 mol%) in Et₂O:C₆F₆ (3:1) at -30°C . ^g Reaction using **1d** (10 mol%) in C₆F₆ at 6°C . ^h Reaction using **1a** (5 mol%) in toluene at -78°C .



yields and enantioselectivities, a thioester substitution led to inferior enantiocontrol (**4d**). It should be highlighted that the more sterically hindered triisopropylsilyl (TIPS) substitution at the dienol derivative provided a slightly improved enantioselectivity, furnishing **4a** in 96:4 e.r. Moreover, substitution on the diene-unit was also tolerated. The 2-methyl dienol **3e** gave rise to the β,β -disubstituted product **4e** in a 90:10 e.r., whereas substitution at the C-3 position led to a decrease in both the yield and the enantioselectivity (**4f**). Remarkably, the γ -methyl derivative built the product **4g** as a 1:6 diasteromeric mixture and at an excellent 97.5:2.5 e.r. (major isomer).

Next, the scope of the quinazoline was examined (Table 2, middle). The method tolerated a variety of groups, proceeding remarkably smoothly with the 7-alkyl and aryl substituted quinazolines. Thus, the dearomatised products **4h** and **4i–k** were obtained with excellent enantiocontrol, no matter the electronic nature of the substituent. An olefin conjugated system or the versatile pinacolatoboron (Bpin) moiety were likewise well-suited, building the desired products **4l** and **4m** with excellent enantioselectivities. Unexpectedly, even when full conversion of 7-methoxyquinazoline into its stabilized *N*-acyl iminium ion was observed, **4n** was not formed and the starting quinazoline was mostly recovered after workup. Conversely, reaction with halogenated 7-bromo and 7-fluor quinazolines led to the corresponding substituted adducts **4o** and **4q** with very good enantioselectivities (up to 97:3 e.r.), while the nitro group showed significantly lower enantiocontrol (**4r**). Moreover, substitution at positions 6 (**4p**) and 5 (**4s**) was also compatible. Moreover, in order to extend the applicability of the method, other heteroarenes such as quinoline, pyridine and 4-chromenone¹⁵ derivatives were also enrolled (see the ESI† for more details), providing the corresponding products **5–7** in moderate to good enantioselectivities. The absolute configuration of the newly formed stereocentre was unequivocally assigned as (*R*) using X-ray crystallographic analysis of the quinazoline product **4k** (see Table 2 and the ESI†).¹⁶ The same stereochemical outcome was assumed for all the compounds of this series.

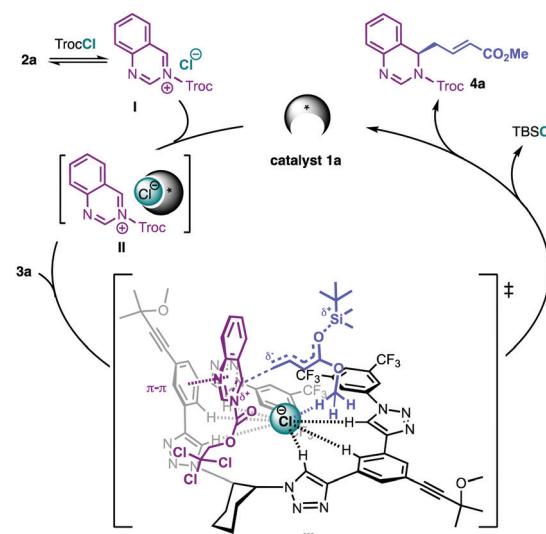
To our delight, upscaling the model reaction of quinazoline (**2a**) 10 times (1 mmol vs. 0.1 mmol) led to a remarkable enhancement in the efficiency of the process (Scheme 2, top). In this case, the TIPS-dienolate **3b** that led to the best enantioselectivity was employed, providing the desired product in a significantly higher yield (83% vs. 59%), while no erosion of the enantioselectivity of the process was observed. In addition, to further prove the utility and applicability of the method, we showed the possibility of recovering the catalyst from the reaction mixture (in 90% yield) and re-using it (Scheme 2, middle). Hence, a subsequent reaction with the recovered catalyst gave similar results in terms of both yield and enantioselectivity (see entry 10, Table 1). We next investigated the synthetic value of the obtained multifunctional chiral quinazoline derivatives with respect to the presence of the α,β -unsaturated system introduced through the vinylogous addition. Thus, the *N*-deprotection of **4a** (0.5 mmol, 96:4 e.r.) with Zn followed by selective hydrogenation of the conjugated double bond led to the



Scheme 2 Upscaling of the reaction, catalyst recovery/reusability and derivatisation towards ring-fused systems.

interesting chiral lactam derivative **8** after *in situ* cyclisation without significant erosion of the enantiopurity of the final product (Scheme 2, bottom).

Finally, evolving from earlier reports,^{4,13} a plausible mechanism that explains the observed enantioselectivity outcome of this vinylogous asymmetric anion-binding catalytic reaction is proposed (Scheme 3). After the *in situ* generation of the substrate of the reaction, the quinazolium salt **I**, upon treatment of quinazoline with TrocCl, a chiral contact ion pair **II** between catalyst **1a** and **I** by anion-binding to its counteranion is formed. A plausible transition state (**III**) presenting multiple interactions of the chiral contact ion pair complex **II** with both reactants can then be envisioned. Thus, the cationic substrate **I** is fixed *via* coulomb attractions with the anionic **1a**-Cl complex and π - π stacking with one arm of the catalyst. In addition, the



Scheme 3 Proposed mechanism.



TBS-dienolate **3a** shows hydrogen-bonding with the chloride counteranion, orientating its distal δ -carbon towards the C4 position of the substrate¹⁷ and allowing for the selective vinylogous nucleophilic attack of the more accessible Re-face of the quinazolinium moiety. Hence, (*R*)-**4a** is obtained as the major product, with concomitant formation of TBSCl.

In conclusion, we have described the first enantioselective organocatalysed vinylogous Mukaiyama-type reaction for the dearomatisation of heteroarenes under anion binding catalysis. The process takes place with high enantiocontrol (up to 97.5:2.5 e.r.) and with a range of differently substituted quinazolines, which could be extended to other types of N- and O-heterocycles. In addition, different experiments and studies such as catalyst recovery/reusability and the derivatisation of the final products have been performed in order to further illustrate the utility and applicability of the presented method.

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Conflicts of interest

There are no conflicts to declare.

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