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Enantioselective synthesis of functionalized 1,4-dihydropyrazolo-[4′,3′:5,6]pyrano[2,3-*b*]quinolines through ferrocenyl-phosphine-catalyzed annulation of modified MBH carbonates and pyrazolones†

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An enantioselective synthesis of highly functionalized 1,4-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-*b*]quinolines from modified MBH carbonates and pyrazolones *via* a chiral phosphine-mediated alkylation/annulation sequence has been realized. The chiral dihydropyrano[2,3-*c*]pyrazoles bearing bio-active condensed heterocycles were facilely formed in good chemical yields and with high to excellent enantioselectivity by utilizing low catalyst loading.

The development of efficient annulation strategies for the construction of heterocycles, due to their peculiar features, has been a longstanding interest of the chemical and pharmaceutical communities.[1,2] Pyrazolones and pyrazoles are significant heterocycles involving a broad range of valuable biological properties.[1e,2b] As an oxygen heterocycle, the dihydropyran scaffold is also a general structural unit broadly existing in numerous biologically active natural products.[3] Among a number of dihydropyran and pyrazole derivatives, the skeletons of 1,4-dihydropyrano[2,3-*c*]pyrazoles that possess both cores of dihydropyran and pyrazole are peculiarly of synthetic and pharmaceutical interest because of their significant potential in pharmaceutical science (Fig. 1).[4]

Pyrazolones have been around for more than one century and have emerged as a commonly-used and versatile synthon to furnish a series of potentially bioactive pyrazole and pyrazolone derivatives.[2b,5] The pyrazolone mostly serves as a brilliant nucleophile in the reactions of carbon–carbon bond formation, especially the Michael addition reactions.[5a–c] There is the existence of either the carbonyl form or the aromatic pyrazole form as a result of tautomerism. However, in solution, the pyrazolone form plays a dominant role. Consequently, the most conventional applications of those scaffolds in organocatalyzed cyclization are shining the spotlight on [1+*n*] and [3+*n*] annulation to achieve highly functionalized heterocycles.[5] Despite the extensive utility of pyrazolones as nucleophiles in asymmetric organocatalysis,[5] their utilization in phosphine-catalyzed transformations,[6] to the best of our knowledge, is rare.[7] It should be noteworthy that Lu and co-workers disclosed the phosphine-mediated [4+1] annulation process to achieve an enantioselective synthesis of spiropyrazolones from pyrazolones and allenoate-derived MBH acetates (Scheme 1a).[7] When it comes to asymmetric [3+3] annulation and related sequential reaction to construct high functionalized dihydropyrans,[8] it has not been realized *via* chiral phosphine catalysis. A represented strategy that amine-catalyzed asymmetric [3+3] annulations of β′-acetoxy allenoates and pyrazolone to enantioselective access diversified 4*H*-pyrans was reported by Tong and co-workers (Scheme 1b).[8a] At present, the related organocatalyzed cyclization of pyrazolones to form chiral dihydropyrano[2,3-*c*]pyrazoles bearing bio-active condensed heterocycles is unknown, resulting in the need for efficient synthetic approaches to this challenging structural motif, particularly for developing a versatile method *via* phosphine catalysis.

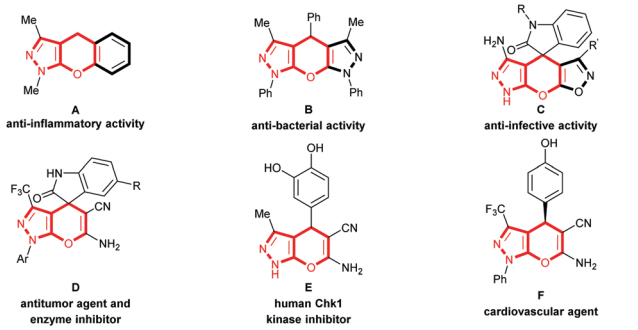

Fig. 1 Biologically active 1,4-dihydropyrano[2,3-c]pyrazole compounds.

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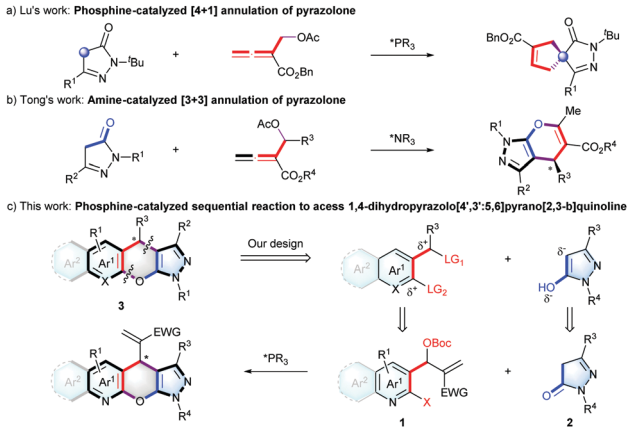
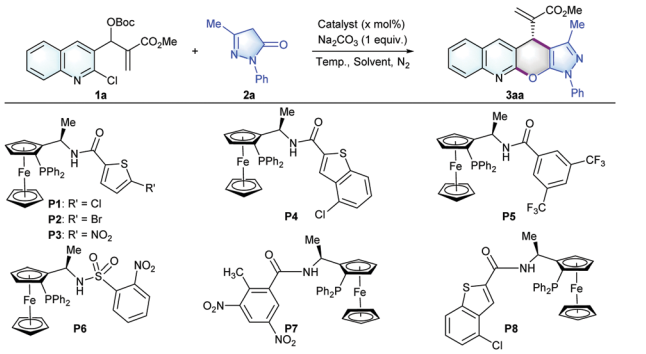


Scheme 1 Asymmetric annulations of pyrazolones.

We envisioned that the complicated structural motifs might be concisely assembled through a phosphine-mediated [3+3] annulation or related sequential reaction. The equilibrium of pyrazole and pyrazolone suggests that it may be a suitable synthon in the proposed annulation. By utilizing a modified Morita–Baylis–Hillman (MBH) carbonate **1** containing a leaving group on the *ortho*-position as a reaction partner, the designed 1,4-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-*b*]quinoline **3** could be facilely achieved (Scheme 1c). In recent years, we have disclosed a series of enantioselective processes promoted by ferrocene-based chiral phosphines.[9] Inspired by our continuous interest in ferrocenyl-phosphine catalysis, we herein describe the straightforward alkylation/annulation sequence of functionalized MBH carbonates **1** and pyrazolones **2** to construct optically enriched 1,4-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-*b*]quinolines **3**.

We first investigate the feasibility of our designed annulation process. Toward this end, methyl 2-(((*tert*-butoxycarbonyl)oxy)(2-chloroquinolin-3-yl)methyl)acrylate **1a** and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **2a** were treated with triphenylphosphine and Na_2CO_3 in toluene at room temperature. Gratifyingly, the cyclization took place smoothly, and the desired product **3aa** was obtained in 88% yield (Table 1, entry 1). Then, our previously designed bifunctional chiral ferrocenylphosphine **P1** was subjected to the asymmetric annulation and the desired product **3aa** was furnished in 50% yield and with excellent enantioselectivity (98% ee) (Table 1, entry 2). Next, to testify the efficiency of phosphine catalysts, various ferrocene-derived bifunctional phosphine catalysts were investigated (Table 1, entries 3–9). Phosphine amide **P4** proved to be a promising catalyst, leading to the formation of the corresponding product **3aa** in 60% yield and with 98% ee (Table 1, entry 5). In the presence of a sulfonamide-derived bifunctional ferrocenylphosphine, only trace annulation product **3aa** was obtained, which demonstrated that the fragment of amide was essential (Table 1, entry 7). Having identified **P4** as the best catalyst, solvent screening was then followed (Table 1, entries 10–12). To our delight, when 1,2-dichlorobenzene (*o*-DCB) was utilized as the solvent, the yield was improved to 73% and the enantioselectivity could reach 95% ee (Table 1, entry 12). Next, the excellent results in terms of the yield and enantioselectivity could also be achieved by increasing the reaction temperature to 40 °C

Table 1 The optimization of the reaction conditions[a]

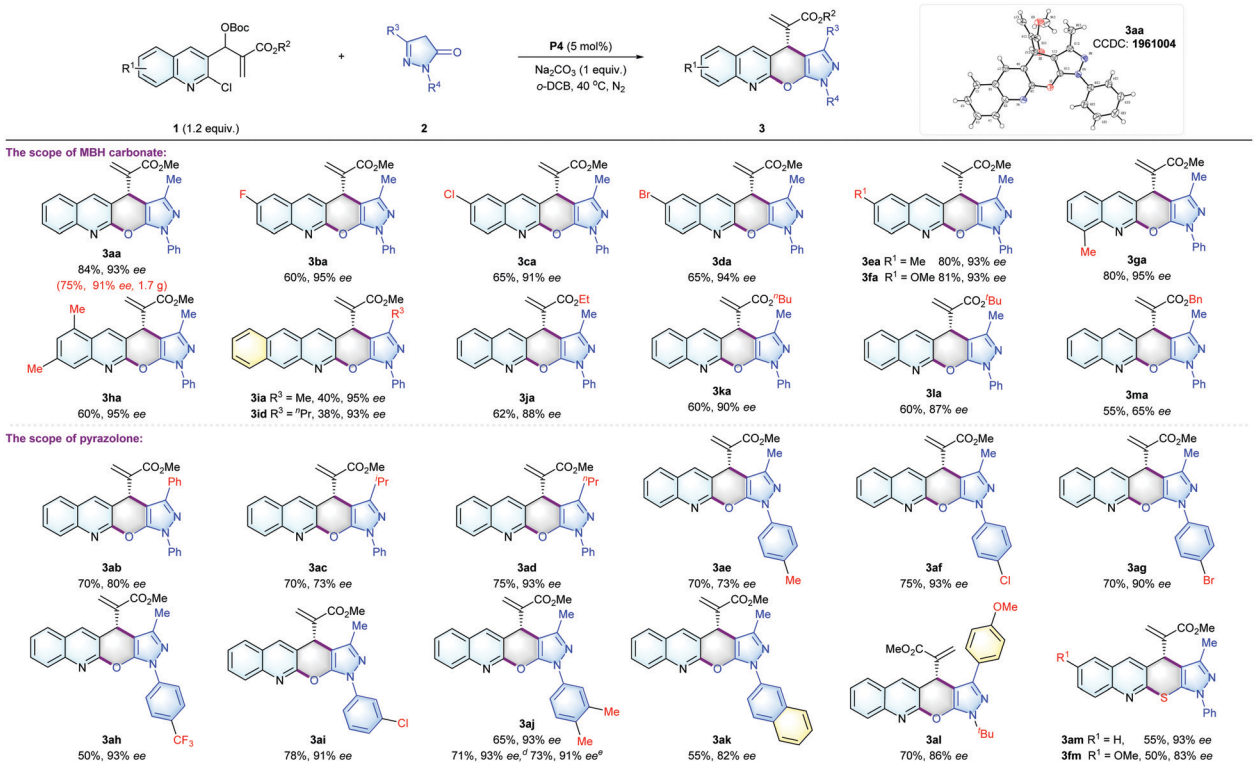


Entry	Cat.	Solvent	*X*	Temp. (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	PPh_3	Toluene	20	25	20	88	—
2	**P1**	Toluene	20	25	96	50	98
3	**P2**	Toluene	20	25	96	52	97
4	**P3**	Toluene	20	25	96	48	98
5	**P4**	Toluene	20	25	96	60	98
6	**P5**	Toluene	20	25	96	55	98
7	**P6**	Toluene	20	25	96	Trace	n.d.
8	**P7**	Toluene	20	25	96	18	−93
9	**P8**	Toluene	20	25	96	50	−98
10	**P4**	*o*-Xylene	20	25	96	62	83
11	**P4**	*o*-DCB	20	25	96	73	95
12	**P4**	TCM	20	25	96	48	84
13	**P4**	*o*-DCB	20/10	40	36/56	86/84	91/93
14	**P4**	***o*-DCB**	**5**	**40**	**72**	**83**	**93**
15[d]	**P4**	*o*-DCB	5	40	72	70	94

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), catalyst (5–20 mol%), Na_2CO_3 (1.0 equiv.) in solvent (2.5 mL), 36–96 h, under N_2 atmosphere. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Using the related MBH acetate to instead of **1a**.

(entries 13 and 14). Ultimately, decreasing the catalyst loading of the reaction did not inhibit the efficiency of forming the desired product, which could afford the compound **3aa** in 83% yield and with 93% ee (entry 14). Changing the reported MBH acetate as the substrate to this reaction, product **3aa** could be obtained in moderate yield (entry 15).

With the optimized reaction conditions in hand, we next commenced to establish the scope of this sequential annulation process (Scheme 2). When it came to functionalized MBH carbonates, the substituted quinolines bearing the functional groups of fluoro, chloro, bromo, methyl, and methoxyl were well-tolerated in this annulation, which could be transformed to the corresponding products in good yields and with excellent enantioselectivity (**3aa–3ga**). The absolute configurations of the desired products were confirmed based on a single-crystal *X*-ray analysis of a derivative of **3aa**.[10] The substrate possessing dimethyl substituent on the quinoline ring was smoothly converted to the product **3ha** in 60% yield and with 95% ee (**3ha**). Even when the condensed heterocycle-substituted MBH carbonate was used, the high ee was still secured (**3ia**, and **3id**). Subsequently, the modified MBH carbonates bearing different ester groups on the side chain proceeded smoothly under the standard conditions (**3ja–3ma**). It was noteworthy that the ee value of the dihydropyran **3ma** derived from benzyl acrylate was the lowest among the products **3ja** to **3ma**, probably owing to



Scheme 2 Asymmetric synthesis of 1,4-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-*b*]quinolines **3**. [a]Reaction condition: **1** (0.6 mmol), **2** (0.5 mmol), P4 (5.0 mol%), Na_2CO_3 (1.0 equiv.) in *o*-DCB (2.5 mL), 72–168 h, under N_2 atmosphere. [b]Isolated yields. [c]Values of ee were determined by using chiral HPLC. [d]**P4** (10 mol%) was added. [e]**P4** (20 mol%) was added.

the π–π interaction influence from the substrate and phosphine **P4**. We further investigated the scope of pyrazolones. Increasing steric hindrance of the groups adjoined to the nucleophilic site of the pyrazolones led to lower enantioselectivity (**3ab–3ad**). Variation of the N substituent on pyrazolone showed that both electron-rich and -deficient aryl groups were well-tolerated (**3ae–3ak**). The *N-tert*-butyl-substituted pyrazolone was then utilized to smoothly afford product **3al** in 70% yield and with 86% ee. Significantly, this strategy could also facilitate the generation of the 1,4-dihydropyrazolo[4′,3′:5,6]thiopyrano [2,3-*b*]quinolone derivatives with high efficiency (**3am** and **3fm**). To further test the practical utility, gram-scale operation was performed by utilizing 6.9 mmol of **1a** and 5.8 mmol of **2a**, which furnished the desired product **3aa** in good yield (75%, 1.7 grams) and with 91% ee (Scheme 2, **3aa**).

Moreover, the investigations on the potential bioactivity of selected chiral 1,4-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-*b*]quinoline derivatives **3** were carried out by testing their cytotoxicity utilizing the MDA-MB-231 breast cancer cell line, A549 human non-small cell lung carcinoma cell line and HT-29 colorectal cancer cell line (for details, see page S35 of the ESI†). Among these compounds (Fig. 2), **3fa** possessed the highest cytotoxicity toward both the MDA-MB-231 (IC_{50} = 3.00 μM) and A549 (IC_{50} = 1.90 μM) cell line. Notably, the derivative **3ba** served as a high-efficacy agonist with low micromolar activities in the HT-29 colorectal cancer cell line (IC_{50} = 4.06 μM). These results indicated that these 1,4-dihydropyrazolo[4′,3′:5,6]pyrano [2,3-*b*]quinoline scaffolds have the potential for drug discovery.

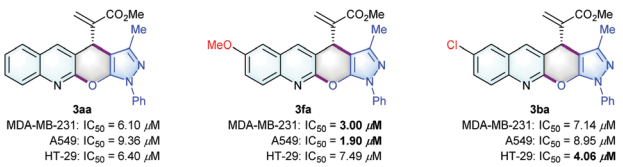
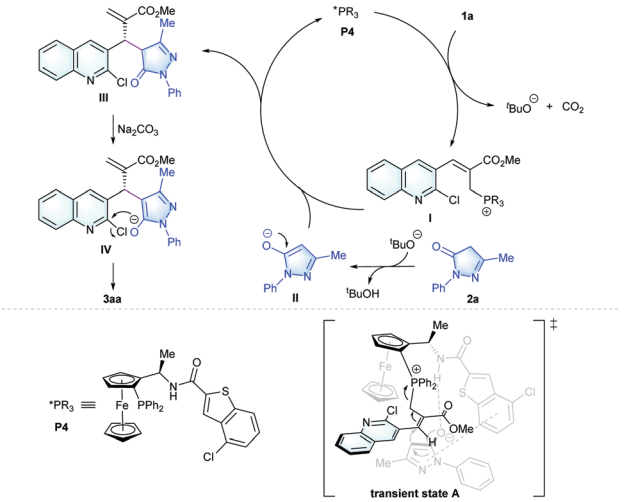


Fig. 2 The bioactivity of chiral 1,4-dihydro pyrazolo[4′,3′:5,6]pyrano[2,3-*b*]quinoline derivatives.

A tentative mechanism for this sequential annulation reaction of designed MBH carbonates and pyrazolones is shown in Scheme 3. Initially, the chiral phosphine **P4** attacks the MBH carbonate **1a** to generate the phosphonium **I** with the release of *tert*-butoxide anion and carbon dioxide, followed by a Michael addition of species **II** to **I** *via* the transient state **A** and then leading to generation of intermediate **III**. A deprotonation is subsequently conducted to generate anion **IV**. An intramolecular S_NAr substitution ultimately took place, resulting in the formation of highly enantioselective 1,4-dihydropyrazolo[4′,3′:5,6]pyrano[2,3-*b*]quinoline derivative **3aa**. In order to illuminate the high yield and enantioselectivity of this transformation, a probable transient state **A** was proposed. Firstly, the phosphine core would be to control the reactivity of MBH carbonate. Secondly, both the H-bonding interaction with the N–H of the amide and the π–π interaction with the benzothiophene on catalyst **P4** to the species **II** would be increasing not only the reaction enantioselectivity but also the reactivity of pyrazolone.



Scheme 3 The plausible mechanism.

In conclusion, we have established a new straightforward methodology for enantioselective synthesis of highly functionalized chiral 1,4-dihydro pyrazolo[4′,3′:5,6]pyrano[2,3-*b*]quinoline derivatives from the newly modified MBH carbonates and pyrazolones *via* ferrocene-derived bifunctional phosphine-catalyzed asymmetric alkylation/annulation sequence. With this strategy, numerous chiral heterocyclic compounds bearing bio-active pyrazoles and quinolines are facilely furnished by utilization of low catalyst loading. The gram-scale operation and potential bioactivity investigation make this synthetic route more useful for pharmaceutical discovery. A more systematic study of both the mechanism and cytotoxicity testing is ongoing.

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Conflicts of interest

There are no conflicts to declare.

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10 CCDC 1961004 contains the supplementary crystallographic data for this paper†.