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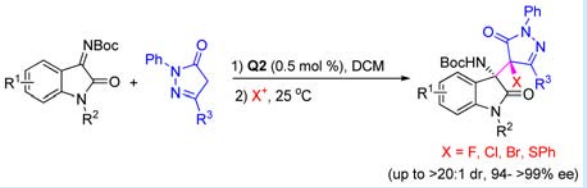
An Organocatalytic Asymmetric Friedel–Crafts Addition/Fluorination Sequence: Construction of Oxindole–Pyrazolone Conjugates Bearing Vicinal Tetrasubstituted Stereocenters

Xiaoze Bao, Baomin Wang,* Longchen Cui, Guodong Zhu, Yuli He, Jingping Qu, and Yuming Song

State Key Laboratory of Fine Chemicals, School of Pharmaceutical Science and Technology, Dalian University of Technology, Dalian 116024, P. R. China

Supporting Information

ABSTRACT: A highly efficient and practical one-pot sequential process, consisting of an organocatalytic enantioselective Friedel–Crafts-type addition of 4-nonsubstituted pyrazolones to isatin-derived *N*-Boc ketimines and a subsequent diastereoselective fluorination of the pyrazolone moiety, is developed. This reaction sequence delivers novel oxindole–pyrazolone adducts featuring vicinal tetrasubstituted stereocenters with a 0.5 mol % catalyst loading in high yield with excellent enantio- and diastereocontrol. Notably, chloro, bromo, and thioether functionalities can be readily incorporated, rendering a broad diversity of the product.



Research efforts toward the development of novel chemical structures have always been welcome and encouraged by the medicinal and agrochemical communities, as these endeavors often hold great potential for the discovery of new drug leads. In this context, studies based on modifications of privileged pharmacophores are especially appealing due to the established biological activities of the parent core structures. Oxindole and pyrazolone scaffolds represent privileged heterocyclic structures and pharmacophores found in a variety of biologically active natural products and medicinal agents (Figure S-1).[1,2] Inspired by the pharmaceutical importance and hence the synthetic value of these species, recent years have seen intense efforts toward the construction of enantiomerically enriched chiral 3,3-disubstituted oxindoles[1a−c,3] and 4,4-disubstituted pyrazolones.[4]

Despite these efforts, however, the construction of vicinal tetrasubstituted stereocenters incorporated into the oxindole[1a−c,5−7] or pyrazolone scaffolds in a highly stereoselective manner remains a remarkably challenging task, and methods toward this goal are very rare, mainly due to the inherent difficulties associated with the assembly of such a sterically congested structural arrangement. To date, very limited approaches to oxindoles incorporating fully substituted adjacent stereogenic centers have been developed starting from 3-substituted oxindoles[6] or isatins.[7] In contrast, access to pyrazolone entities with such a stereodiad is even rarer, with only one example being reported.[8] Hence, when considering the formidable challenge within this topic coupled with the significant pharmaceutical relevance of oxindole and pyrazolone scaffolds, the development of highly efficient, enantio- and diastereoselective methods leading to the expeditious buildup of vicinal tetrasubstituted stereocenters featuring oxindole and/or pyrazolone skeletons is arguably in high demand.

Very recently, isatin-derived ketimines have risen to prominence owing to their versatile electrophilic reactivity, leading to a wide variety of enantioenriched 3-amino quaternary oxindole products.[9,10] In this context, noteworthy is that elegant contributions from the groups of Feng,[10a] Shao,[10b] Wennemers,[10c] and others[10d−f] realized the assembly of vicinal tetrasubstituted stereogenic structures. Despite the elegance of these reports, in general, the simultaneous formation of both stereocenters in a single-step reaction with a tertiary carbon nucleophile through the orchestration of a chiral promoter restricts the variability of the substituents attached to the quaternary carbon center outside the oxindole ring (Scheme 1). To address this deficiency and to broaden the diversity of the stereocenters generated, we envisioned a one-pot stereoselective sequential transformation involving an organocatalytic enantioselective Friedel–Crafts-type addition of pyrazolones to isatin-derived *N*-Boc ketimines and a further diastereoselective functionalization of the pyrazolone moiety (Scheme 1). This simple one-pot operation takes advantage of the double nucleophilic reactivity of the 4-nonsubstituted pyrazolone species and would lead to the construction of a novel oxindole–pyrazolone conjugate bearing vicinal tetrasubstituted stereocenters in a highly stereoselective manner. More interestingly, by varying the electrophile of the second step, a wide variety of different tetrasubstituted pyrazolone carbon centers could potentially be achieved, thereby significantly extending the diversity of the stereodiads. Herein, we document our research efforts toward the validation of this concept.

The one-pot reaction sequence of the Friedel–Crafts addition of pyrazolone **2a** to isatin-derived *N*-Boc ketimine **1a** followed by fluorination with *N*-fluorobenzenesulfonimide (NFSI) was selected as a testing system to define the optimal conditions (Table 1). An initial brief screening of chiral organic base

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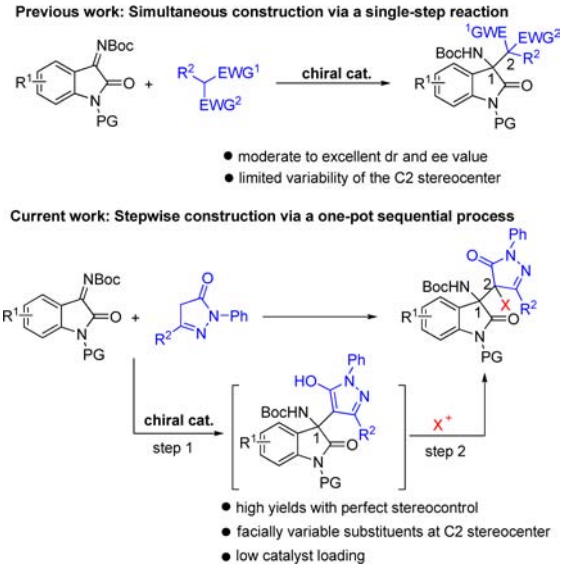
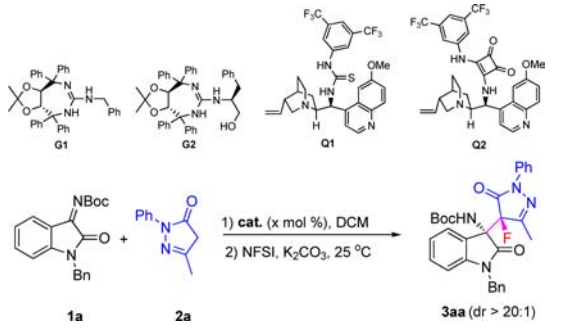
Scheme 1. Strategies to Construct 3-Amino Oxindoles with Vicinal Tetrasubstituted Stereocenters[a]



[a]PG = protecting group, EWG = electron-withdrawing group.

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	x	time[b]	yield (%)[c]	ee (%)[d]
1	**quinine**	10	41 h	95	50
2	**G1**	10	14 h	94	59
3	**G2**	10	27 h	94	23
4	**Q1**	10	30 min	95	>99
5	**Q2**	10	10 min	94	>99
6	**Q2**	2	20 min	94	>99
7	**Q2**	0.5	1.5 h	93	>99
8	**Q2**	0.1	9 h	92	97
9[e]	**Q2**	0.5	2 h	93	>99
10[e]	**Q1**	0.5	9 h	94	97

[a]Unless otherwise noted, reactions were conducted with **1a** (0.1 mmol), **cat.** (*x* mol %), **2a** (0.12 mmol) in solvent (1.0 mL). After **1a** was consumed, K_2CO_3 (0.15 mmol) and NFSI (0.15 mmol) were added, and the mixture was stirred for 1 h at 25 °C. [b]Time for the first step. [c]Isolated yield. [d]Ee determined by chiral HPLC analysis; dr determined by ^{1}H NMR of the crude reaction mixture. [e]**2a** (0.11 mmol), K_2CO_3 (0.13 mmol), and NFSI (0.13 mmol) were used.

catalysts revealed that both tartrate-derived guanidines[11] developed recently by us and cinchona alkaloids can effectively catalyze the reaction with excellent yields and varying degrees of enantiocontrol (Table 1, entries 1−3). It is interesting to note that uniformly high diastereoselectivities of over 20:1 dr were always observed on forging the fluorine-containing quaternary center in the fluorination event with NFSI and K_2CO_3.

Compared to tartrate-based guanidines **G1**, **G2** and natural quinine, to our great pleasure, the well-established quinine thiourea catalyst **Q1** exhibited excellent reactivity and perfect stereocontrol, affording the oxindole−pyrazolone conjugate with vicinal N- and F-containing quaternary centers in 90 min (30 min for the first step) with a 95% yield and a more than 99% enantiomeric excess (entry 4). Notably, an even better reactivity was observed with quinine squaramide catalyst **Q2**, which accomplished the addition step in only 10 min (entry 5). Given the extremely high reactivity of **Q2**, reactions with lower catalyst loadings were investigated. Interestingly, with 2 mol % **Q2**, still a very fast reaction was observed, completing the addition step in 20 min without any loss of the yield or stereoselectivity for the whole transformation (entry 6). Remarkably, further reducing the loading to 0.5 mol % had no impact on the yield and stereoselectivity, only with a modest extension of the reaction time to 1.5 h (entry 7). Particularly noteworthy is that even a very low catalyst loading of 0.1 mol % could also afford an excellent result of 92% yield and 97% ee, though a 9-h period was needed to drive the addition step to completion (entry 8). It should be stressed that such a low catalyst amount is among the very rare examples of low-loading organocatalysis.[12] In consideration of the rate and stereoselectivity, 0.5 mol % **Q2** was used in the following studies. In addition, the stoichiometries of pyrazolone **2a**, NFSI, and K_2CO_3 can be reduced without compromising the outcome (entry 9). A comparison experiment confirmed the superiority of **Q2**, as **Q1** exhibited lower reactivity and enantioselectivity under otherwise identical conditions (entry 10 vs 9).

With the optimal conditions being identified, the substrate generality with respect to both the isatin ketimine and pyrazolone components was evaluated. The results were summarized in Figure 1, which indicates that a broad spectrum of isatin *N*-Boc ketimines and pyrazolones were amenable to the sequential addition/fluorination process, affording a diverse array of oxindole−pyrazolone conjugates bearing vicinal N- and F-containing quaternary centers in uniformly high yields with perfect stereocontrol. In most cases, essentially enantiopure products were obtained.

Initially, *N*-substitution of the oxindole nitrogen was investigated (Figure 1, **3aa**−**3da**). Interestingly, other than the benzyl group, methyl and allyl substituents were well accommodated. In addition, nonprotected free NH on the oxindole ring was also tolerated (**3da**), which allows for facile potential *N*-substitutions on demand. Next, with *N*-benzyl protection, substitution on the benzene ring of the oxindole frame was evaluated. It was found that both electron-withdrawing halogen atoms and electron-donating methyl and methoxy substituents were well accommodated, achieving the same levels of excellence in efficiency and stereoselectivity (**3ea**−**3ia**).

Following the establishment of the broad generality of the isatin ketimine component, the substrate scope with respect to the pyrazolone partner was surveyed. Similarly, a broad array of pyrazolones were demonstrated to be competent substrates, affording excellent yields and perfect stereoselectivities with high efficiency (**3ab**−**3am**). Specifically, various substituents at the C3 position of the pyrazolone ring were broadly accommodated, including alkyl, benzyl, aryl, and heteroaryl groups. Of note is the tolerance to the cyclopropyl group (**3ad**), a pharmaceutically relevant structure motif.[13] In addition, the presence of allyl, chloro, and bromo functional groups in the product molecules provides useful synthetic handles for further derivatization, thereby potentially enhancing the structural diversity of the

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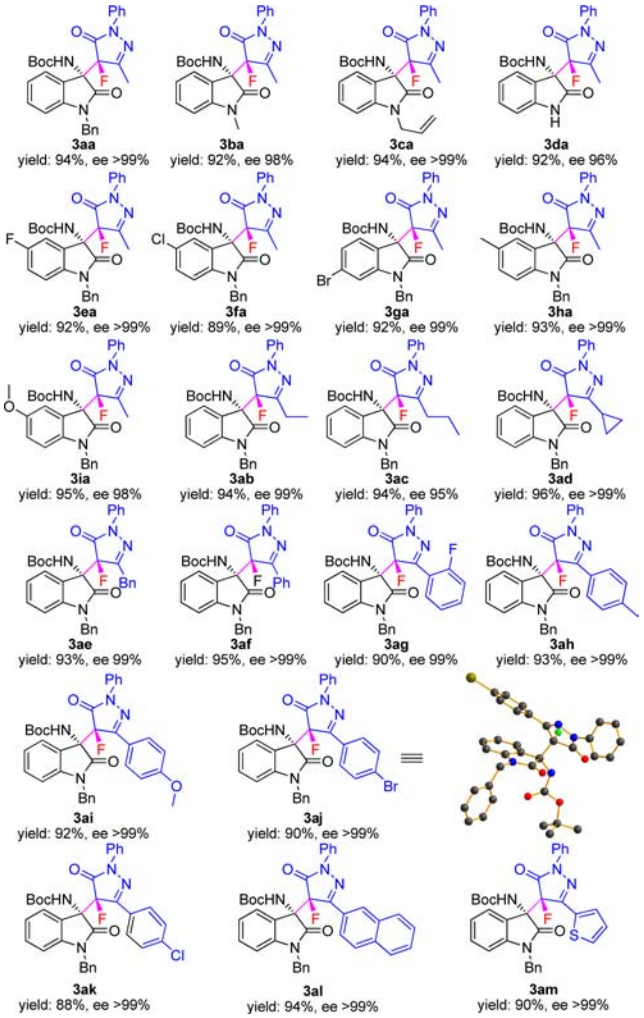


Figure 1. Generality of the Friedel–Crafts addition/fluorination sequence; dr > 20:1 for all cases.

product. Owing to the low catalyst loading of the process, a gram-scale synthesis of **3aj** was readily achieved with maintained efficiency and stereoselectivity (eq 1), thus highlighting the practical utility of the current reaction.

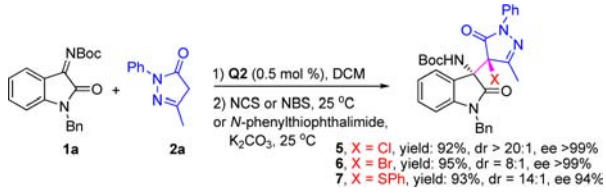
The absolute stereochemistry of product **3aj** was determined to be (3*S*, 4′*R*) by X-ray crystallographic analysis,[14] and those of other products were assigned by analogy. In order to elucidate the stereochemical course of the sequential process, a two-pot experiment was investigated. Thus, upon completion of the addition of **2a** to **1b**, the intermediate product **4** was isolated in 95% yield and 99% ee (Scheme 2), which clearly indicates that the first step is enantioselective. Then, exposure of **4** to NFSI and K_2CO_3 in the absence of the chiral catalyst **Q2** delivered the final product **3ba** in 92% yield, with 98% ee and over 20:1 dr (Scheme 2). This result firmly demonstrates that the second step is diastereoselective, and the diastereoselectivity of the fluorination

Scheme 2. Elucidation of the Stereochemical Course of the Sequential Process

event is independent of the chiral catalyst, but a pure substrate-controlled result.[15]

The stepwise sequential nature of the current process and the independence of the diastereocontrol on the chiral catalyst make it possible to vary the electrophiles in the second step, thereby expanding the diversity of the vicinal tetrasubstituted stereogenic structures. As proof of concept, the enantioselective Friedel–Crafts addition of pyrazolone **2a** to isatin ketimine **1a** was readily combined with diastereoselective chlorination and bromination processes by simple *N*-chloro- and *N*-bromosuccinimide (Scheme 3), respectively, with high yield and excellent

Scheme 3. Variability of the Vicinal Tetrasubstituted Stereocenters



stereoselectivity. Furthermore, the sequential process is also amenable to the introduction of a thioether structure, as demonstrated by the capture of the addition product by *N*-phenylthiophthalimide, giving the vicinal quaternary-center product in 93% yield, 14:1 dr, and 94% ee (Scheme 3). Given the reported reactivity of 4-substituted pyrazolones,[4] the synthetic potential of the current strategy may be considerably expanded.

In conclusion, a highly efficient and practical one-pot sequential process, consisting of an organocatalytic enantioselective Friedel–Crafts-type addition of 4-nonsubstituted pyrazolones to isatin-derived *N*-Boc ketimines and a subsequent diastereoselective functionalization of the pyrazolone moiety, is developed. This reaction sequence delivers novel oxindole–pyrazolone adducts featuring vicinal tetrasubstituted stereocenters in high yield with excellent enantio- and diastereocontrol. Additional salient features include a very low catalyst loading of 0.5 mol %, mild reaction conditions, ease of operation, facile scale-up, and broad substrate scope. Most importantly, the flexible variability of the electrophiles employed in the second step coupled with the independence of the diastereocontrol on the chiral catalyst allows for a broad diversity of the product, as exemplified by the facile incorporation of fluoro, chloro, bromo, and thioether functionalities into the product molecules. Studies directed toward extending the scope of the sequential process and evaluating the biological activities of the oxindole–pyrazolone conjugates are currently underway in our laboratory, and the results will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02470.

Experimental procedures and detailed characterization data of all new compounds (PDF)
X-ray crystal details for **3aj** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bmwang@dlut.edu.cn.

Notes

The authors declare no competing financial interest.

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(14) The structure of **3aj** is also shown in Figure S-2 in the Supporting Information. CCDC 1415232 contains the supplementary crystallographic data for **3aj**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) The stepwise reaction pathway and the plausible stereochemical working models for the sequential process are proposed. See Scheme S-1 in the Supporting Information for details.

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