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Organocatalytic Atroposelective Construction of Axially Chiral Compounds Containing Benzimidazole and Quinoline Rings

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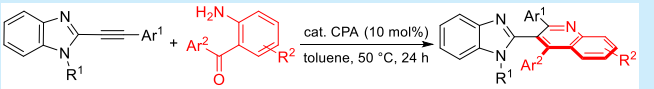
ABSTRACT: An organocatalytic atroposelective strategy for the construction of axially chiral compounds containing benzimidazole and quinoline rings is described. The enantioselective heteroannulation reaction of 2-alkynylbenzimidazoles with *ortho*-aminophenylketones proceeded smoothly in the presence of chiral phosphoric acid to provide axially chiral heterobiaryls with good yields and enantioselectivities. This is the first example of the combination of benzimidazole and quinoline rings at the 2- and 3-positions, respectively, into axially chiral heterobiaryls by this new strategy.

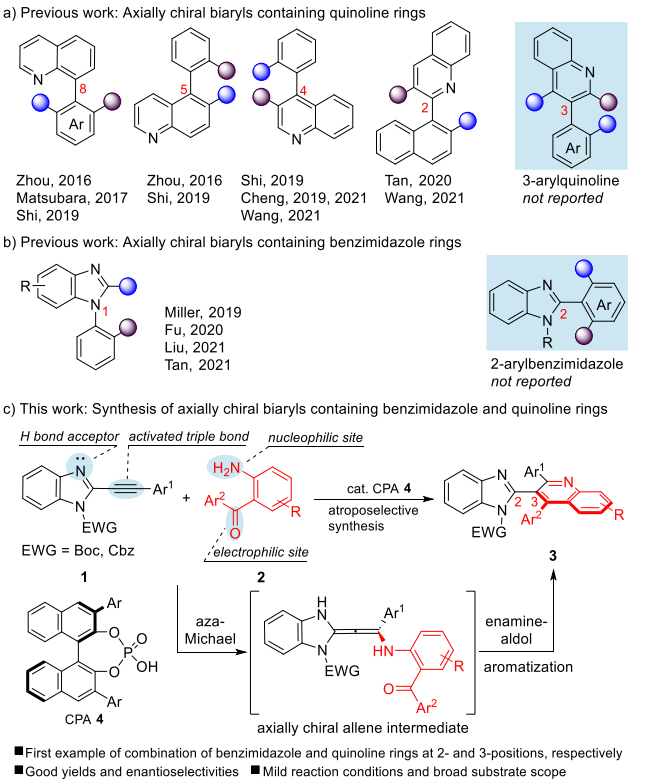


First example of combination of benzimidazole and quinoline rings at 2- and 3-positions, respectively

Axially chiral biaryl frameworks are frequently found not only in natural products[1] and pharmaceuticals[2] but also in privileged chiral ligands[3] and catalysts.[4] Therefore, the development of convenient and efficient methods for the construction of diverse axially chiral biaryls has attracted considerable attention over the past decades.[5] In comparison with typical aromatic axially chiral compounds, such as biphenyls and binaphthyls,[6] examples of heteroaromatic axially chiral compounds, particularly benzimidazole and quinoline ring-containing axially chiral compounds, have rarely been reported.[5d,7] The synthesis of 2-, 4-, 5-, and 8-aryl axially chiral quinolines has been accomplished through the kinetic resolution of axially chiral 5- or 8-aryl quinolines via asymmetric transfer hydrogenation,[8] the enantioselective modification of 8-aryl quinolines by aromatic electrophilic halogenation[9] or aromatic C−H olefination,[10] the enantioselective Suzuki−Miyaura cross-coupling reaction of aryl boronic acids with 5- or 8-bromoquinolines,[11] and the organocatalytic atroposelective heterocycloaddition of 2-aminoaryl ketones/aldehydes with 1,3-dicarbonyl compounds[12] or alkynes (Scheme 1a).[13] To the best of our knowledge, only a few studies on the synthesis of 1-aryl axially chiral benzimidazoles, which involved organocatalytic atroposelective heterocycloaddition[14] or enantioselective intramolecular Buchwald−Hartwig reaction, have been reported (Scheme 1b).[15] In the above examples, the N−C chiral axis was constructed, while the benzimidazole rings were formed. However, as far as we know, the synthesis of 3-aryl axially chiral quinolines and 2-aryl axially chiral benzimidazoles is unprecedented (Scheme 1a and 1b).

Quinoline and benzimidazole moieties are present in a wide range of bioactive molecules that display broad-spectrum pharmacological activities,[16] and they also constitute the central core of various ligands.[17] Therefore, the development of a convenient and efficient method for the construction of axially chiral compounds containing benzimidazole and quinoline rings is highly desirable.

Scheme 1. Axially Chiral Biaryls Containing Benzimidazole and/or Quinoline Rings



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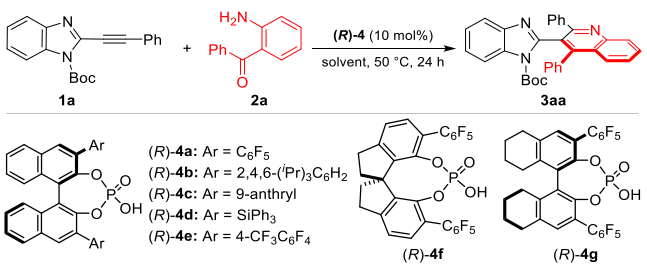
In the current work, we designed and synthesized 2-alkynyl benzimidazole substrates **1** bearing an electron-withdrawing group (EWG) at the N1-position for heteroannulation with 2-aminoaryl ketones **2** to obtain a new type of axially chiral heterobiaryl compound **3** (Scheme 1c). The C−C triple bond introduced at the 2-position of the benzimidazole unit functions as an efficient Michael acceptor because of the introduction of EWG into the N1-position, thereby facilitating the intended enantioselective heteroannulation reaction under the influence of a chiral catalyst. The proposed reaction design is outlined in Scheme 1c. Aza-Michael type addition of amine **2** to 2-alkynyl benzimidazole **1** affords an axially chiral allenyl intermediate in an enantioenriched form using chiral phosphoric acid (CPA) **4** as a chiral Brønsted acid catalyst.[4a,c,18] The subsequent intramolecular enamine-aldol reaction in an enantio-specific manner followed by aromatization completes the proposed heteroannulation reaction. Here we report the catalytic enantioselective heteroannulation reaction of **1** with **2** using CPA **4** as a chiral catalyst, giving rise to a new type of axially chiral heterobiaryl compound **3** in an enantioenriched form.

In our initial studies, the reaction of 1-*tert*-butyloxycarbonyl-2-phenylethynylbenzimidazole (**1a**) with 2-benzoylphenylamine (**2a**) was selected as a model to optimize the reaction conditions. The results are shown in Table 1 (for details, see the Supporting Information). The organocatalyst, CPA **4**, was screened in toluene at 50 °C for 24 h (entries 1−7). The intended heteroannulation reaction gave the desired product **3aa** in 65% yield with 40% *ee* when BINOL-derived CPA (*R*)-**4a** bearing two electron-withdrawing substituents (C_6F_5) at the 3- and 3′-positions was examined (entry 1). The BINOL-derived CPAs (*R*)-**4b**, (*R*)-**4c**, and (*R*)-**4d** bearing sterically bulky substituents (2,4,6-(^{i}Pr)$_3$C$_6$H$_2$, 9-anthryl, and $SiPh_3$), respectively, were subsequently investigated, and no satisfactory results were obtained (entries 2−4, 10%−21% yields, 27%−59% *ee*). These results indicated that increasing the steric hindrance effect of the CPA catalysts was not conducive to catalyzing the intended reaction. To our delight, the yield and *ee* of product **3aa** were eventually dramatically increased to 77% and 91%, respectively, by utilizing BINOL-derived CPA (*R*)-**4e** bearing stronger electron-withdrawing substituents (4-$CF_3C_6F_4$) as the catalyst (entry 5). No reaction was observed when SPINOL-derived CPA (*R*)-**4f** was tested (entry 6). In comparison with the results in entry 1, almost the same yield was observed when H8-BINOL-derived CPA (*R*)-**4g** was examined as the catalyst, but the *ee* decreased to 28% (entry 7). The solvents were then screened using (*R*)-**4e** as the catalyst. Among the solvents (toluene, dichloromethane [DCM], Et_2O, tetrahydrofuran [THF], $CHCl_3$, MeCN, *p*-xylene, and C_6H_5Cl) examined, toluene proved to be the best solvent for obtaining an excellent *ee* value (entries 8−14 vs entry 5). The effect of the ratio of **1a** to **2a** on the reaction yield was finally investigated. The yield of product **3aa** was not considerably increased, although 2.0 equiv of **2a** were used (entry 15 vs entry 5).

Table 1. Screening of Reaction Conditions[a]



Entry	CPA cat. (*R*)-**4**	Solvent	Yield (%)[b]	*ee* (%)[c]
1	(*R*)-**4a**	toluene	65	40
2	(*R*)-**4b**	toluene	21	59
3	(*R*)-**4c**	toluene	20	27
4	(*R*)-**4d**	toluene	10	29
5	(*R*)-**4e**	toluene	77	91
6	(*R*)-**4f**	toluene	NR[d]	none
7	(*R*)-**4g**	toluene	67	28
8[e]	(*R*)-**4e**	DCM	38	80
9[e]	(*R*)-**4e**	Et_2O	60	45
10	(*R*)-**4e**	THF	15	50
11	(*R*)-**4e**	$CHCl_3$	30	81
12	(*R*)-**4e**	MeCN	50	54
13	(*R*)-**4e**	*p*-xylene	90	89
14	(*R*)-**4e**	C_6H_5Cl	77	89
15[f]	(*R*)-**4e**	toluene	80	89

[a]Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.1 mmol), **2a** (1.5 equiv, 0.15 mmol), and (*R*)-**4** (10 mol %) in 1.0 mL of solvent at 50 °C for 24 h. [b]Isolated yield. [c]The *ee* value of **3** was determined by HPLC analysis using a chiral stationary phase. [d]No reaction; the starting materials were recovered. [e]The reaction was performed at 40 °C. [f]The reaction was performed using 2.0 equiv of **2a** (0.2 mmol).

Under optimal conditions, the scope and generality of 2-arylethynylbenzimidazole derivative **1** were investigated. The results are listed in Scheme 2. The reactions of **1b**−**1e** bearing an electron-donating group (Me and OMe) or a relatively weak EWG (F and Br) at the *para*-position of the benzene ring proceeded smoothly, similar to the reaction of **1a**. The desired axially chiral biaryl compounds **3ba**−**3ea** were obtained in a range of 70%−92% yields with 70%−88% *ee*. However, a dramatically decreased *ee* was observed when a strong EWG (CF_3) was introduced at the *para*-position of the benzene ring in the 2-arylethynylbenzimidazole substrate (**3fa**: 71% yield, 37% *ee*), presumably because of the high reactivity of substrate **1f** in the nucleophilic addition step with **2a** (Scheme 5). A sharply decreased *ee* was subsequently found when *para*-phenyl-substituted substrate **1g** was utilized (**3ga**: 64% yield, 13% *ee*). This low *ee* value may be caused by a relatively strong steric hindrance effect. Neither an electron-donating group (Me and OMe) nor a weak EWG (F and Cl) introduced at the *meta*-position of the benzene ring influenced the reaction yields and *ee*. The desired products **3ha**−**3ka** were isolated in 74%−97% yields with 78%−90% *ee*. With the exception of MeO, the substituents Me, F, and Cl introduced at the *ortho*-positions of benzene rings led to the formation of desired products with relatively low *ee* values owing to the steric hindrance effect. Surprisingly, 91% *ee* was observed for the reaction of *ortho*-MeO-substituted substrate **1m** (**3ma**: 44% yield, 91% *ee*). The free rotation of the O−C(Ar) bond might reduce the steric hindrance effect of MeO. The 2-naphthylethynylbenzimidazole substrates, **1p** and **1q**, were then examined under the standard conditions, and moderate enantioselectivities were observed (**3pa**, 63% *ee*; **3qa**, 50% *ee*). The low yields of **3la** and **3pa** may be attributed to the steric hindrance effect of the *ortho*-positions. The results finally obtained demonstrated that heteroaryl ethynyl-containing substrates **1r** and **1s** were suitable for the intended reaction (**3ra**: 92% yield, 83% *ee*; **3sa**: 70% yield, 76% *ee*).

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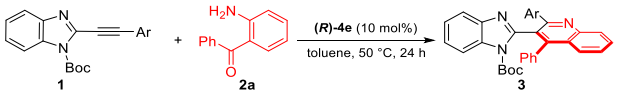
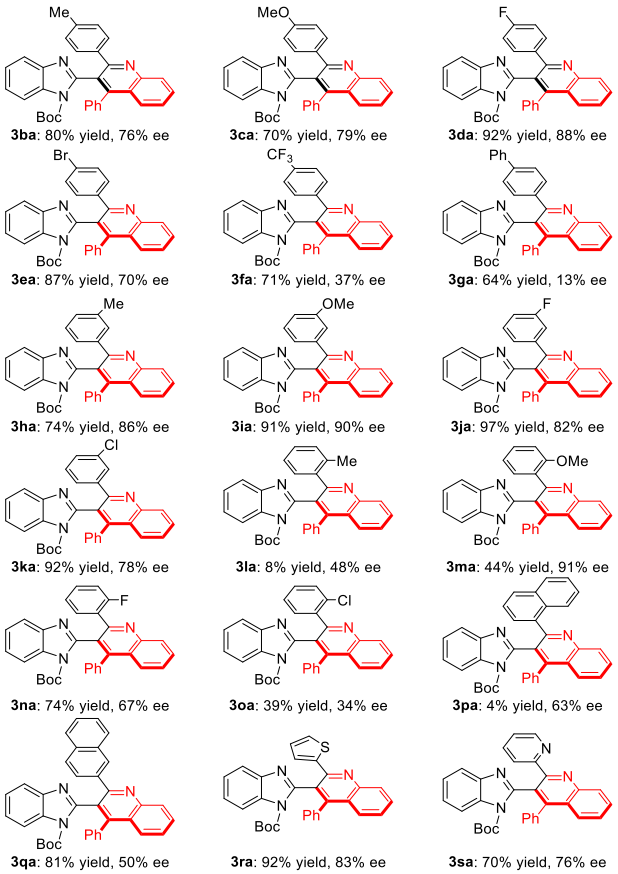
Scheme 2. Scope of 2-Alkynylbenzimidazole Derivatives[a]



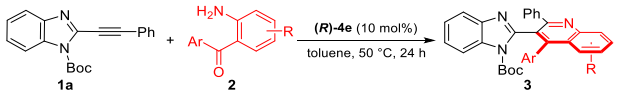


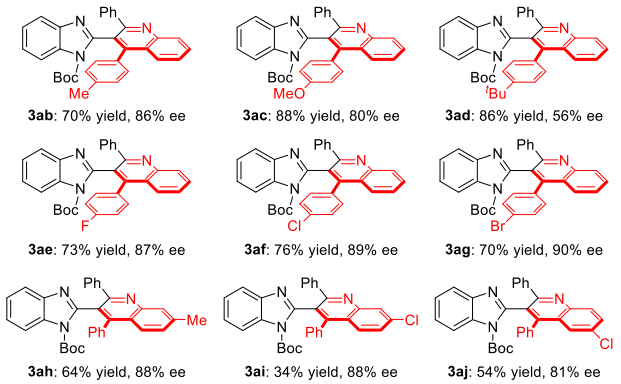
[a]Reaction conditions: all reactions were performed with **1** (0.2 mmol), **2a** (1.5 equiv, 0.3 mmol), and (*R*)-**4e** (10 mol %) in 2.0 mL of toluene at 50 °C for 24 h. Isolated yield. The *ee* value of **3** was determined by HPLC analysis using a chiral stationary phase.

The scope of the *ortho*-aminophenylketone substrate **2** was then investigated using **1a** as the reaction partner. The results are listed in Scheme 3. Reactions of (2-aminophenyl)(*p*-tolyl)methanone (**2b**) and (2-aminophenyl)(4-methoxyphenyl)methanone (**2c**) proceeded smoothly to give axially chiral biaryl compounds **3ab** and **3ac** in 70% and 88% yields with 86% *ee* and 80% *ee*, respectively. The reaction of substrate **2d** bearing a sterically bulky substituent *tert*-butyl also proceeded smoothly to provide the desired product **3ad** in good yield (86%) with moderate *ee* (56%). High yields and excellent enantioselectivities were observed when halogen atom (F, Cl, and Br)-containing substrates **2e**−**2g** were investigated (**3ae**−**3ag**: 70%−76% yields, 87%−90% *ee*). The structure of **3ag** was confirmed through X-ray crystallographic analysis (for details, see the Supporting Information). Finally, substrates **2h**−**2j** bearing a substituent (Me or Cl) on the benzene ring of 2-aminophenyl were examined. Almost the same good enantioselectivities were observed (**3ah**: 88% *ee*; **3ai**: 88% *ee*; **3aj**, 81% *ee*), but a relatively high yield was found for product **3ah**.

Continued substrate extension studies showed that the benzyloxycarbonyl (Cbz) group could be used as an EWG

Scheme 3. Scope of 2-Aminobenzophenone Derivatives[a]

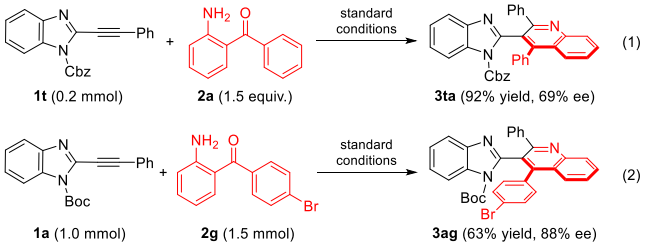




[a]Reaction conditions: all reactions were performed with **1a** (0.2 mmol), **2** (1.5 equiv, 0.3 mmol), and (*R*)-**4e** (10 mol %) in 2.0 mL of toluene at 50 °C for 24 h. Isolated yield. The *ee* value of **3** was determined by HPLC analysis using a chiral stationary phase.

instead of Boc. The reaction of substrate **1t** with **2a** proceeded smoothly under the standard conditions to furnish product **3ta** in 92% yield with 69% *ee* (Scheme 4, eq 1). Large-scale

Scheme 4. Control Experiment and Scale-up Synthesis



synthesis of **3ag** was performed under standard reaction conditions to demonstrate the synthetic practicality and utilization of the new methodology further (Scheme 4, eq 2). To our delight, the desired product **3ag** was obtained in 63% yield with 88% *ee* when the reaction was conducted on a 1.0 mmol scale. The yield and *ee* are comparable to those obtained in the small-scale experiment.

On the basis of our experimental outcomes and previous reports,[19] a catalytic cycle is proposed to account for the present organocatalytic atroposelective annulation reaction (Scheme 5). Initially, catalyst (*R*)-**4e**, **1a**, and **2a** form assembled adduct **A** through a hydrogen bonding interaction. The nucleophilic attack of the amino group in **2a** on an alkyne moiety in **1a** results in the formation of enantioenriched allene derivative **B**. Subsequently, intermediate **B** undergoes an intramolecular enamine-aldol reaction in an enantio-specific manner, affording axially chiral intermediate **C**. The proposed heteroannulation reaction is complete through further dehydration of **D** generated from protonation of the hydroxyl group in **C** by (*R*)-**4e**, resulting in an aromatization to produce enantioenriched heterobiaryl product **3aa** and regenerate (*R*)-**4e**.

In summary, we have successfully developed the first organocatalytic atroposelective construction of axially chiral

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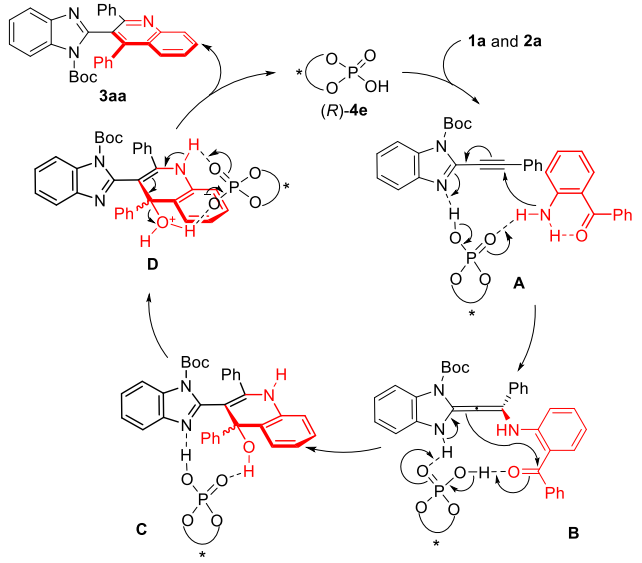
Scheme 5. Proposed Mechanism



compounds containing benzimidazole and quinoline rings. The enantioselective heteroannulation reaction of 2-alkynyl benzimidazoles with *ortho*-aminophenylketones proceeded smoothly in the presence of organocatalyst CPA to provide axially chiral heterobiaryls with good yields and enantioselectivities in most cases (up to 97% yield, 91% *ee*). This is the first example of the combination of benzimidazole and quinoline rings at the 2- and 3-positions, respectively, into axially chiral heterobiaryls using the new strategy. Studies on the practicalities of product **3** and the synthesis of other heterocycle-containing axially chiral heterobiaryls utilizing the new strategy are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01905.

Experimental procedures, characterization data, NMR spectra and mass spectrum, optical data of products, and crystallographic data for **3ag** (PDF)

Accession Codes

CCDC 2261121 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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