RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2019, **9**, 31654

Received 18th July 2019
Accepted 30th September 2019

DOI: 10.1039/c9ra05532k

rsc.li/rsc-advances

Enantioselective bromination of axially chiral cyanoarenes in the presence of bifunctional organocatalysts†

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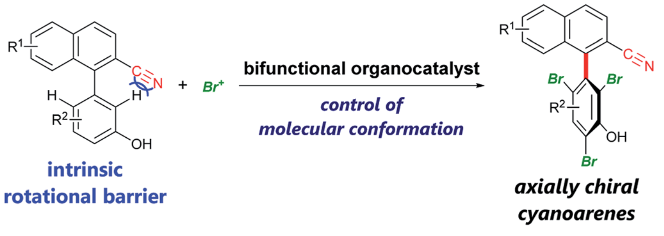
Enantioselective bromination of axially chiral cyanoarenes bearing high intrinsic rotational barriers *via* dynamic kinetic resolution using bifunctional organocatalysts is reported. Sequential addition of a brominating reagent in several portions at an optimized temperature was effective in accomplishing high enantioselectivities.

Axially chiral biaryls are privileged structures in pharmaceuticals,[1] asymmetric catalysts,[2] functional materials,[3] *etc.* Thus, the development of efficient methods for their synthesis is desirable to advance research in these scientific fields. Among recent accomplishments on catalytic atroposelective transformations[4] toward the synthesis of densely substituted axially chiral biaryls, powerful strategies include organocatalytic dynamic kinetic resolution involving *ortho*-functionalization of existing biaryls *via* the introduction of additional rotational barriers.[5] In this method, substrates should in principle have rotational barriers low enough to enable fast rotation about the biaryl axis, leading to their rapid racemization. Therefore, it is difficult to employ biaryl substrates bearing intrinsic rotational barriers, which impede their racemization. In 2015, the Miller group reported an elegant example of this type of dynamic kinetic resolution *via* bromination of 3-arylquinazolin-4(3*H*)-ones, the rotational barrier of which is ~19 kcal mol^{-1}, by slow addition of a brominating agent.[5e] Here, we present enantioselective bromination of axially chiral cyanoarenes bearing intrinsic rotational barriers exceeding 18 kcal mol^{-1} (Scheme 1). To the best of our knowledge, there has been no report of a catalytic asymmetric reaction affording axially chiral cyanoarenes,[6] despite their prevalence in bioactive agents[7] and the rich chemistry of cyano compounds as synthetic intermediates.[8]

Table 1 shows the optimization of reaction conditions. We started our investigation using 1-(3-hydroxyphenyl)-2-naphthonitrile (**1a**) and *N*-bromoacetamide (NBA, **4a**) as the brominating reagent with 10 mol% quinine-derived bifunctional catalysts **3a–3c** in CH$_2$Cl$_2$ at 25 °C. Urea and amide catalysts **3a** and **3c**, respectively, afforded **2a** in higher enantioselectivities than the thiourea catalyst **3b** (Table 1, entries 1–3).[9] Other catalysts **3d** and **3e**, bearing a cyclohexanediamine framework, and **3f**, bearing a binaphthyl framework, resulted in poor enantioselectivities (Table 1, entries 4–6).[10] Using **3a** and **3c**, lower reaction temperatures were investigated (Table 1, entries 7–10); **3c** gave higher enantioselectivity at −40 °C, although the reactions did not proceed at all at −60 °C. By screening different solvents, CH$_2$Cl$_2$ was identified as the most suitable solvent from the viewpoints of both yield and enantioselectivity (Table 1, entries 9 and 11–16). Other brominating reagents (Fig. 1) were also investigated; NBA (**4a**) still afforded the best enantioselectivities (Table 1, entries 9 and 17–19). The decrease in the loading of **3c** to 5 mol% slightly improved the enantioselectivity, although a longer reaction time (48 h) was necessary (Table 1, entry 20). Next, using the thus-optimized conditions, reactions with shorter reaction times (24 h, 12 h, and 6 h) were carried out (Table 1, entries 21–23); the enantioselectivity was improved while the conversions decreased with decreasing reaction time. These results imply that the racemization of **1a** at −40 °C is not rapid enough to make use of dynamic kinetic resolution.



Scheme 1 Enantioselective bromination of axially chiral cyanoarenes using bifunctional organocatalysts.

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† Electronic supplementary information (ESI) available: Experimental procedures, analytical and spectroscopic data for synthetic compounds, and copies of NMR. CCDC 1936455. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra05532k

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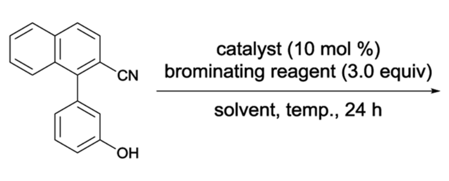
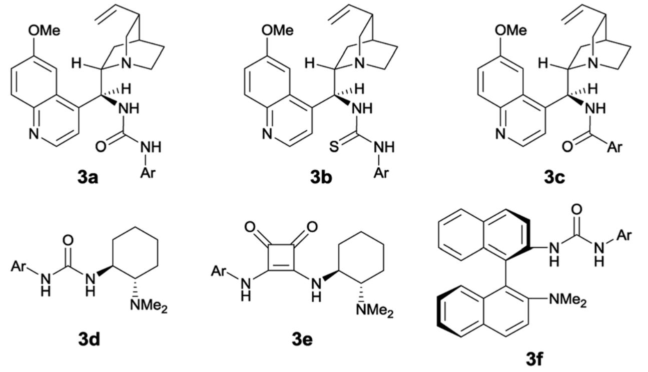
Table 1 Optimization of conditions[a]



1a **2a**

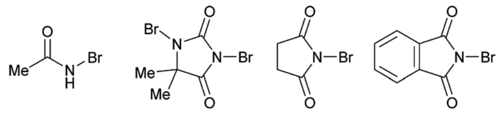
Entry	Catalyst	Brominating reagent	Solvent	Temp. (°C)	Yield[b] (%)	ee (%)
1	**3a**	NBA (**4a**)	CH_2Cl_2	25	81	26
2	**3b**	NBA (**4a**)	CH_2Cl_2	25	87	6
3	**3c**	NBA (**4a**)	CH_2Cl_2	25	89	18
4	**3d**	NBA (**4a**)	CH_2Cl_2	25	83	6
5	**3e**	NBA (**4a**)	CH_2Cl_2	25	85	3
6	**3f**	NBA (**4a**)	CH_2Cl_2	25	79	3
7	**3a**	NBA (**4a**)	CH_2Cl_2	−40	82	20
8	**3a**	NBA (**4a**)	CH_2Cl_2	−60	<1	—
9	**3c**	NBA (**4a**)	CH_2Cl_2	−40	83	41
10	**3c**	NBA (**4a**)	CH_2Cl_2	−60	<1	—
11	**3c**	NBA (**4a**)	$CHCl_3$	−40	21	54
12	**3c**	NBA (**4a**)	Toluene	−40	18	−10
13	**3c**	NBA (**4a**)	THF	−40	13	−2
14	**3c**	NBA (**4a**)	Et_2O	−40	46	−20
15	**3c**	NBA (**4a**)	EtOAc	−40	68	−4
16	**3c**	NBA (**4a**)	EtOH	−40	<5	—
17	**3c**	DBH (**4b**)	CH_2Cl_2	−40	79	1
18	**3c**	NBS (**4c**)	CH_2Cl_2	−40	82	20
19	**3c**	NBP (**4d**)	CH_2Cl_2	−40	79	−5
20[c,d]	**3c**	NBA (**4a**)	CH_2Cl_2	−40	85	49
21[c,e]	**3c**	NBA (**4a**)	CH_2Cl_2	−40	51	59
22[c,f]	**3c**	NBA (**4a**)	CH_2Cl_2	−40	33	66
23[c,g]	**3c**	NBA (**4a**)	CH_2Cl_2	−40	17	71



3a **3b** **3c** **3d** **3e** **3f**

Ar = 3,5-$(CF_3)_2C_6H_3$

[a] Reactions were run using **1a** (0.10 mmol), the brominating reagent (0.30 mmol), and the catalyst (0.010 mmol) in the solvent (10 mL). [b] Isolated yields. [c] Reactions were run using **3c** (0.0050 mmol). [d] Reaction was run for 48 h. [e] Reaction was run for 24 h. [f] Reaction was run for 12 h. [g] Reaction was run for 6 h.



NBA (**4a**) DBH (**4b**) NBS (**4c**) NBP (**4d**)

Fig. 1 Brominating reagents.

Subsequently, to improve the efficiency of dynamic kinetic resolution by retarding the enantiodetermining bromination,[5e] **4a** was added sequentially in five portions (Fig. 2).[11] Although the procedure hardly affected the results at −40 °C, the enantioselectivity was greatly improved for reactions carried out at −20 °C and −30 °C. Such effects were smaller at temperatures above −10 °C.

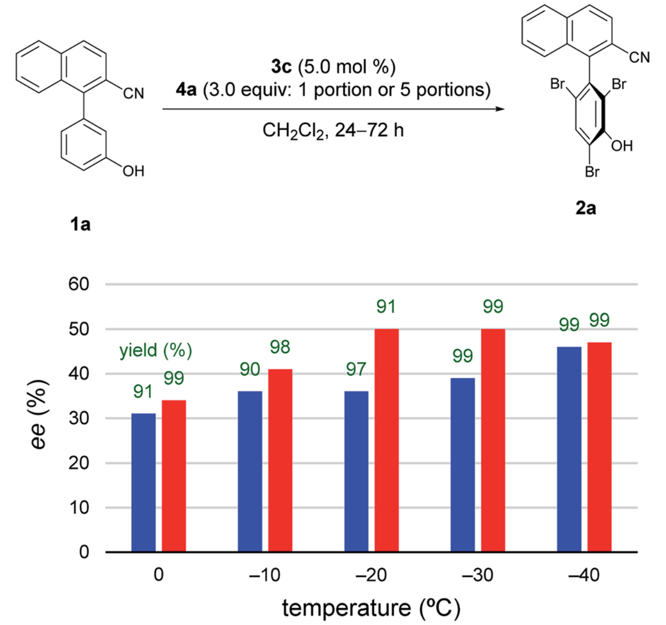


Fig. 2 Investigations of temperatures and procedures. Blue bar: reactions were run with **4a** added in 1 portion. Red bar: reactions were run with **4a** added in 5 portions. Green values represent yields of **2a** isolated after silica gel column chromatography. At 0, −10, −20, and −30 °C, reactions were run for 24 h; at −40 °C, reactions were run for 72 h.

Next, at −30 °C and −40 °C, respectively, the relationships between enantioselectivity and yield were investigated (Fig. 3). Reactions were carried out using various amounts of **4a**. At both temperatures, the enantioselectivity decreased as the yield increased; however, the quantitative reactions also exhibited some enantioselectivity (−30 °C: 99% yield, 50% ee; −40 °C: 99% yield, 47% ee), implying the presence of the characteristics of dynamic kinetic resolution. In addition, although the enantioselectivity was better at −40 °C than −30 °C when the yield was low, the relationship became reversed as the yield increased; hence, the efficiency of dynamic kinetic resolution was revealed to be better at −30 °C than at −40 °C. Furthermore, when 1.5 equiv. of **4a** were used at −30 °C affording **2a** in 22% yield with 65% ee, the *ortho*-monobrominated product **1a**-Br (Fig. 4) was also obtained with 75% ee (see Scheme S1 in the ESI† for details). It shows that the bromination at one of the *ortho*-positions introduces a rotational barrier high enough to set the chiral axis, which is consistent with the rotational barriers calculated at the M06-2X/6-311++G(2d,3p)//B3LYP/6-31+G(d,p) level of theory (Fig. 4).

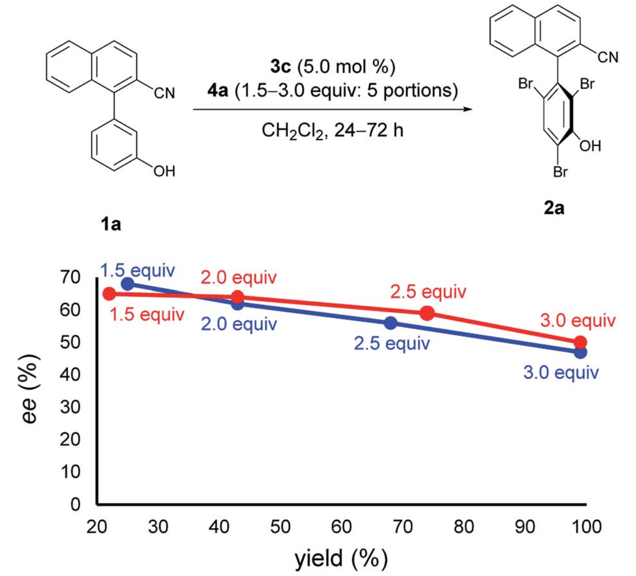


Fig. 3 Relationships between ee and yield. Red line: reactions were run at −30 °C for 24 h with **4a** added in 5 portions. Blue line: reactions were run at −40 °C for 72 h with **4a** added in 5 portions. Red and blue values represent amounts of **4a** used for each reaction.

Under the conditions of using **3c** as the catalyst at −30 °C with 3 equiv. of **4a** added sequentially in five portions, other substrates bearing substituted phenols were also investigated (Scheme 2).[12] First, substrates **1b–1e** bearing a substituent at the *meta*-position were investigated. While the electron-deficient substrate **1b** resulted in poor enantioselectivity, **1c** and **1d** bearing aliphatic substituents gave improved enantioselectivities; however, substrate **1e** with a methoxy group resulted in low enantioselectivity. In addition, substrates **1f–1i** bearing substituents at the *para*-positions of the biaryl axis were then examined; phenol **2h** bearing a methyl group resulted in higher enantioselectivities than phenols **2f** and **2g** bearing electron-withdrawing groups and **2i** bearing a methoxy group. These results suggest that aliphatic substituents might efficiently facilitate the racemization of **1** during bromination, leading to dynamic kinetic resolution with greater enantioselectivity. Utilizing this methodology with the characteristics of dynamic kinetic resolution, the reactions of **1c** and **1g** were also carried out using a sub-stoichiometric amount of **4a** (Scheme 3); higher enantioselectivities were accomplished albeit with lower yields.[13] The absolute configuration of **2c** was determined by X-ray crystallography (see the ESI† for details), and the configurations of all other products were assigned analogously.

In summary, we present enantioselective bromination of axially chiral cyanoarenes bearing high intrinsic rotational barriers *via* dynamic kinetic resolution using bifunctional

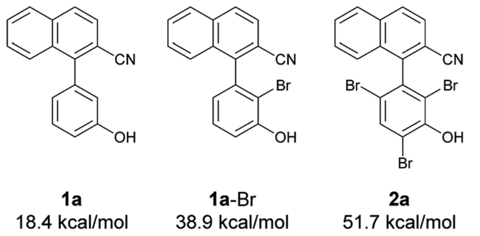
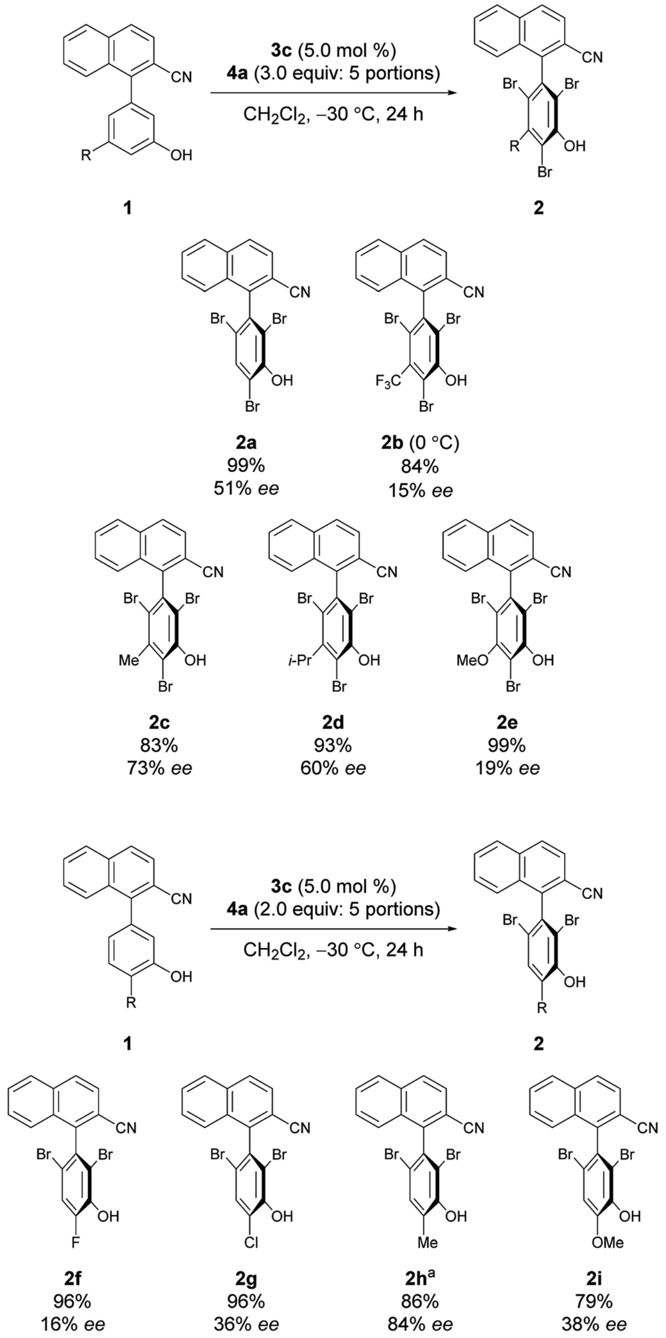
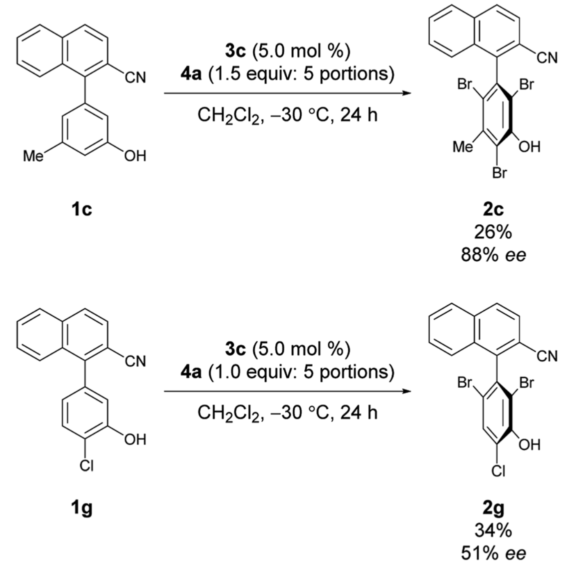


Fig. 4 Rotational barriers of substrate, intermediate, and product calculated at the M06-2X/6-311++G(2d,3p)//B3LYP/6-31+G(d,p) level of theory.



Scheme 2 Reactions of substrates with substituted phenols. ^{a}Reaction was run for 72 h.

organocatalysts. The sequential addition of **4a** in several portions at the optimized temperature was effective in improving the enantioselectivity. Although the enantioselectivities are still moderate using the current catalytic system, the guidelines for designing catalytic asymmetric syntheses of axially chiral cyanoarenes were established. Further studies on the additional optimization and application of this methodology to the construction of densely substituted axially chiral biaryls are currently underway.



Scheme 3 Reactions with a substoichiometric amount of **4a**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported financially by the Japanese Ministry of Education, Culture, Sports, Science and Technology (JP15H05845, JP16K13994, JP17K19120, JP18K14214, and JP18H04258). K. A. also acknowledges the Naito Foundation, Research Institute for Production Development, the Tokyo Biochemical Research Foundation, the Uehara Memorial Foundation, the Kyoto University Foundation, the Institute for Synthetic Organic Chemistry, Toyo Gosei Memorial Foundation, the Sumitomo Foundation, and Fukuoka Naohiko Memorial Foundation. A. M. also acknowledges the Japan Society for the Promotion of Science for Young Scientists for the fellowship support.

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9 The replacement of the cyano group with an ethynyl group in **1a** gave much lower enantioselectivity in the presence of **3c**; the replacement of the NH group with an NMe group in **3c** gave much lower enantioselectivity and catalytic activity in the reaction of **1a**; the replacement of the OH group with an OMe group in **1a** resulted in no reaction in the presence of **3c**. These results suggest that the cyano and OH groups of **1a** and the NH group of **3c** are involved in hydrogen bonding between **1a** and **3c** during catalysis. See Scheme S2 in the ESI† for details.

10 Results of further catalyst screening are described in the ESI (Table S1†).

11 Slow addition of **4a** over hours resulted in low yields, probably because **4a** was decomposed in its CH_2Cl_2 solution in the syringe while addition after being left for a while.

12 It was difficult to prepare substrates bearing substituted 2-naphthonitriles.

13 The reaction of **1h** using 0.5 equiv. of **4a** afforded an *ortho*-monobrominated product in 43% yield with 81% ee (see Scheme S3 in the ESI† for details), which is not higher than the result (84% ee) obtained in Scheme 2. These results also imply that aliphatic substituents increase the efficiency of dynamic kinetic resolution.