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Asymmetric Synthesis of 2,3-Dihydroquinolin-4-one Derivatives Catalyzed by a Chiral Bisguanidium Salt

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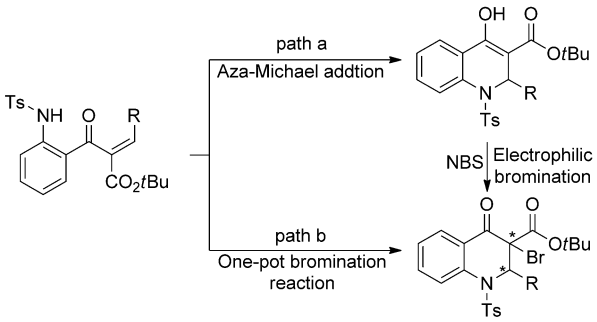
Optically active 2,3-dihydroquinolin-4-one scaffolds exhibit intriguing biological activities and have attracted significant attention.[1] Among the strategies for the construction of such compounds,[2] asymmetric intramolecular aza-Michael addition of α,β-unsaturated ketones with aniline is a straightforward route. The first example of enantioselective intramolecular aza-Michael addition to afford 2,3-dihydroquinolin-4-ones was reported by You's group with chiral *N*-triflyl phosphoramide.[2c] Later, the Lu group developed a bifunctional thiourea-mediated intramolecular cyclization to achieve this goal.[2d] One limitation of previous work in this area is that 2-alkyl-substituted derivatives could not be obtained with high enantioselectivity. Additionally, synthesis of chiral 2,3-dihydroquinolin-4-one derivatives with vicinal stereogenic centers has not been reported to date. Recently, the Ma group developed a one-pot, multistep transformation to synthesize 3-halo-2,3-dihydroquinolin-4-one derivatives with high diastereoselectivity.[3] Herein, we report an efficient organocatalytic asymmetric intramolecular aza-Michael reaction and a one-pot bromination reaction for the synthesis of optically enriched 2-substituted dihydroquinones and brominated dihydroquinones, respectively (Scheme 1). In the presence of chiral bisguanidium salt catalyst, both 2-aryl- and 2-alkyl-substituted products could be generated with excellent outcomes (up to 99% yield and 99% *ee* for the aza-Michael reaction and up to 95% yield, 96:4 d.r., and 95% *ee* for the one-pot bromination reaction).

To improve the reactivity of the intramolecular aza-Michael reaction, an ester function was added to the unsaturated ketones and a sulfonyl group was attached to the nitrogen of the anilines .[2,4] This additional functionality provided more sites for potential interaction with a catalyst. The stereochemistry of the starting substrates **2** were identified to be *E*-type by X-ray crystallography analysis.[5] In view of



Scheme 1. Intramolecular aza-Michael reaction and one-pot bromination reaction to obtain 2,3-dihydroquinolin-4-one derivatives.

our previous study relating to guanidine[6,7] promoted reactions of 1,3-dicarbonyl compounds and azlactones, we envisioned that this kind of bifunctional organocatalyst[7h–m] could also initiate the intramolecular aza-Michael addition of activated α,β-unsaturated ketone . As shown in Table 1, a series of guanidines and bisguanidines (**1a–e**) were used to promote the asymmetric intramolecular cyclization (Table 1, entries 1–5). In all cases, the reactions were rapid and complete conversion was achieved within 0.5 hour at 25 °C. Chiral bisguanidine **1c** derived from (*S*,*S*)-1,2-diphenylethylenediamine and (*S*)-pipecolic acid emerged as the most promising catalyst, affording the product **3a** in 99% yield with 50% *ee* (Table 1, entry 3). In view of the unique and helpful role of an achiral counterion which can modify the catalyst's reactivity and structure directly,[8] a bisguanidium salt was next evaluated. When the corresponding bisguanidium salt[6i–m] **1c·HBAr$^F_4$** ($HBAr^F_4$ = $HB[3,5\text{-}(CF_3)_2C_6H_3]_4$) was used, the enantioselectivity improved to 58% *ee* (Table 1, entry 6). Catalysts with other counterions were also tested, but no improvement was observed (see the Supporting Information for details). The use of polar solvents resulted in a sharp decline in enantioselectivity, which might be due to the adverse effect on the hydrogen-bonding interactions between the substrate and the catalyst (Table 1, entries 7–9 vs. entry 6). CH_2Cl_2 was the best solvent, generating the product with slightly improved enantioselectivity (Table 1, entry 10). Notably, the *ee* value of the product increased gradually by lowering the reaction temperature (Table 1, entries 10–14). The desired quinolone derivative **3a** could be obtained in 99% yield with 96% *ee* at −60 °C (Table 1, entry 14). It was worth mentioning that the catalyst

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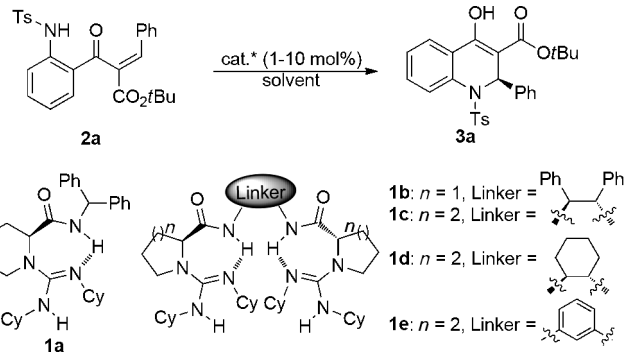
Table 1. Optimization of the reaction conditions in the asymmetric intramolecular aza-Michael reaction.



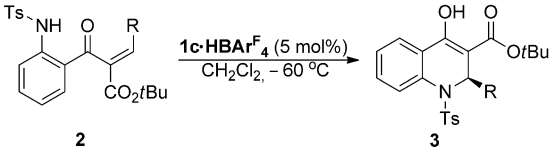
Entry[a]	Cat.	Solvent	t [h]	T [°C]	Yield [%][b]	ee [%][c]
1	**1a**	toluene	0.5	25	99	17
2	**1b**	toluene	0.5	25	99	8
3	**1c**	toluene	0.5	25	99	50
4	**1d**	toluene	0.5	25	99	12
5	**1e**	toluene	0.5	25	99	12
6[d]	**1c·HBAr$^F_4$**	toluene	0.5	25	99	58
7[d]	**1c·HBAr$^F_4$**	THF	0.5	25	99	28
8[d]	**1c·HBAr$^F_4$**	Et_2O	0.5	25	99	28
9[d]	**1c·HBAr$^F_4$**	DMF	0.5	25	99	0
10[d]	**1c·HBAr$^F_4$**	CH_2Cl_2	0.5	25	99	60
11[d]	**1c·HBAr$^F_4$**	CH_2Cl_2	0.5	0	99	84
12[d]	**1c·HBAr$^F_4$**	CH_2Cl_2	0.5	−20	99	86
13[d]	**1c·HBAr$^F_4$**	CH_2Cl_2	2	−45	99	91
14[d]	**1c·HBAr$^F_4$**	CH_2Cl_2	8	−60	99	96
15[d,e]	**1c·HBAr$^F_4$**	CH_2Cl_2	10	−60	99	96
16[d,f]	**1c·HBAr$^F_4$**	CH_2Cl_2	72	−60	99	97

[a] Unless otherwise noted, all reactions were carried out with **1c·HBAr$^F_4$** (10 mol%) and **2a** (0.05 mmol) in solvent (0.5 mL) at the temperature specified. [b] Isolated yield. [c] Determined by HPLC. [d] **HBAr$^F_4$** = $HB[3,5\text{-}(CF_3)_2C_6H_3]_4$. [e] 5 mol% **1c·HBAr$^F_4$** was used. [f] 1 mol% **1c·HBAr$^F_4$** was used.

loading could be decreased to 1 mol% without any loss in the yield and enantioselectivity (Table 1, entry 16) although a longer reaction time was required.

Under the optimized reaction conditions (Table 1, entry 15), various alkylidene β-ketoesters **2** were explored to examine the generality of the reaction. In the presence of chiral bisguanidium salt **1c·HBAr$^F_4$**, a wide range of 2,3-dihydroquinolin-4-one derivatives **3** were generated with high yields (up to >99%) and excellent *ee* values (93–99%). As shown in Table 2, the electronic property and position of the substituent on the aromatic ring of substrate **2** have no significant influence on the enantioselectivity (Table 2, entries 1–9). Substrate **2b** bearing an *ortho*-fluoride substituent led to the cyclized product in good yields and high enatioselectivity, although a significantly longer reaction time was required (98% yield, 94% *ee*; Table 2, entry 2). The 2-naphthyl substituted substrate **2j** was also suitable substrate for the reaction, affording the product **3j** with 99% yield and 96% *ee* (Table 2, entry 10). It is worth noting that substrates containing aliphatic groups delivered the desired 2-alkyl-2,3-dihydroquinones with superior yields and enantioselectivities compared to previous reports[2] (Table 2, entries 11–14).

Table 2. Substrate scope in the asymmetric intramolecular aza-Michael reaction.



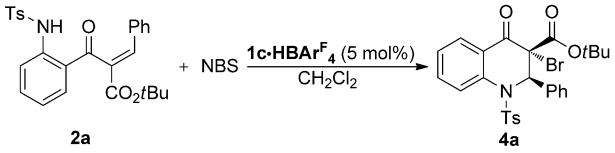
Entry[a]	R	Prod.	t [h]	Yield [%][b]	ee [%][c]
1	Ph	**3a**	10	99	96(*R*)
2	2-FC_6H_4	**3b**	116	98	94(*S*)
3	3-FC_6H_4	**3c**	16	99	96(*R*)
4	4-FC_6H_4	**3d**	28	99	95(*R*)
5	3-ClC_6H_4	**3e**	28	99	93(*R*)
6	4-ClC_6H_4	**3f**	18	99	93(*R*)
7	3-BrC_6H_4	**3g**	24	99	94(*R*)
8	4-BrC_6H_4	**3h**	24	99	93(*R*)
9	4-MeC_6H_4	**3i**	34	99	95(*R*)
10	2-naphthyl	**3j**	14	99	96(*R*)
11	*i*Pr	**3k**	18	99	98(*R*)
12	*n*Pr	**3l**	52	99	95(*R*)
13	*n*-pentyl	**3m**	20	99	94(*R*)
14	*c*-hexyl	**3n**	24	99	99(*R*)

[a] Unless otherwise noted, all reactions were carried out with **1c·HBAr$^F_4$** (5 mol%) and **2a** (0.05 mmol) in CH_2Cl_2 (0.5 mL) at −60°C. [b] Isolated yield. [c] Determined by HPLC.

Alkenes **2k**–**2n** with either linear or branched alkyl substituents were also well tolerated , giving excellent yields and enantioselectivities (93–99% *ee*). Upon treatment with toluene sulfonic acid (TsOH), decarboxylation occured readily to give the corresponding 2,3-dihydro-4-quinolone. The absolute configuration of **3a** was confirmed to be *R* by comparison with the reported value of optical rotation.[2d] The stereochemical arrangement of the products **3b**–**3n** was determined to be identical through the assay of the Cotton effect in the circular dichroism (CD) spectra (see the Supporting Information for details).

Next, we turned our attention to investigate the one-pot synthesis of brominated dihydroquinones.[9] Initially, the reaction between activated α,β-unsaturated ketone **2a** and *N*-bromosuccinimide (NBS) was performed with chiral bisguanidium salt **1c·HBAr$^F_4$** at −20°C in CH_2Cl_2. The desired product **4a** was generated in 94% *ee* and 88:12 d.r., although the reaction time was significantly increased in comparison with the aza-Michael reaction (Table 3, entry 1). Increasing the reaction temperature had no positive effect on the yield or enantioselectivity (Table 3, entry 2). Increasing the concentration had minimal effect on the observed stereoselectivity (Table 3, entry 3). To our delight, the addition of 4 Å molecular sieves (MS) notably increased the reaction rate and allowed the reaction to reach completion within 1 day with 88% yield, 93% *ee*, and 91:9 d.r. (Table 3, entry 4). The absolute configuration of the major product **4a** was determined to be (2*R*,3*R*) by X-ray crystallography analysis (Figure 1a).[5] The decreased isolated yield resulted from the generation of byproduct **5a**, which was formed from the bromination at the C6-position of dihydroquinone

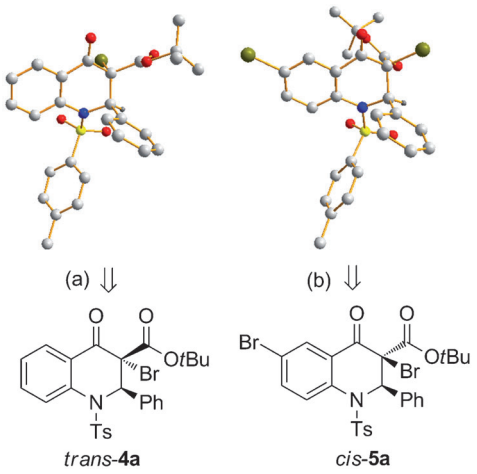
Table 3. Optimization of the reaction conditions in the asymmetric one-pot bromination reaction.



2a 4a

Entry[a]	T [°C]	t [d]	Yield [%][b]	*ee* [%][c]	*trans*/*cis*[d]
1	−20	4	86	94	88:12
2	0	3	82	90	85:15
3[f]	−20	2	79	93	90:10
4[f,g]	−20	1	88	93[e]	91:9

[a] Unless otherwise noted, all reactions were carried out with **1c·HBAr$^{F}_{4}$** (5 mol%), NBS (0.06 mmol) and **2a** (0.05 mmol) in CH_2Cl_2 (0.5 mL) at the temperature specified. [b] Isolated yield. [c] Determined by HPLC. [d] Determined by ^{1}H NMR spectroscopy and HPLC analysis. [e] Absolute configuration of the major product was determined to be (2*R*,3*R*) by X-ray crystallography. [f] The reaction was carried out with **1c·HBAr$^{F}_{4}$** (5 mol%), NBS (0.11 mmol) and **2a** (0.1 mmol) in CH_2Cl_2 (0.15 mL) at −20°C. [g] 4 Å molecular sieves (20.0 mg) were added.



trans-**4a** *cis*-**5a**

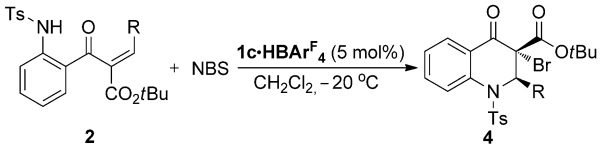
Figure 1. X-ray crystallographic structures of *trans*-**4a** and *cis*-**5a**.

4a. The structure of **5a** was confirmed by X-ray crystallography analysis (Figure 1b).

The general applicability of the one-pot bromination reaction of activated α,β-unsaturated ketones **2** was examined using bisguanidium salt **1c**·HBAr$^{F}_{4}$ at −20°C. As shown in Table 4, in the presence of NBS, a variety of 3-bromo-2,3-dihydroquinolin-4-ones **4** could be obtained in 78–95% yields, 88–95% *ee*, and 78:22–96:4 d.r.. The reaction was unbiased toward both the substitution pattern and electronic properties of the aromatic moiety (Table 4, entries 1–10). but the *ortho*-substituted alkene **2b** exhibited a slightly low reactivity (Table 4, entry 2). Gratifyingly, the fused-ring and aliphatic substrates were successfully employed in the reaction (Table 4, entries 11 and 12). No aza-Michael products **3** were isolated with the exception of the reaction of **2b**.[10]

Interestingly, the *trans* isomer of **4a** could be gradually transformed into the *cis* isomer in toluene which might lead to spontaneous epimerization and crystallization-induced

Table 4. Substrate scope in the asymmetric one-pot bromination reaction.

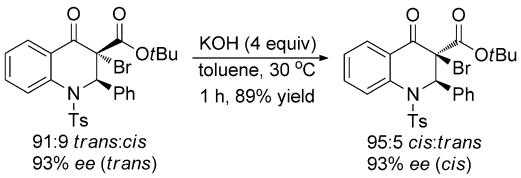


2 **4**

Entry[a]	R	Prod.	t [d]	Yield [%][b]	*ee* [%][c]	*trans*/*cis*[d]
1	Ph	**4a**	1	88	93	91:9
2	2-FC$_6$H$_4$	**4b**	2	78[e]	92	78:22
3	3-FC$_6$H$_4$	**4c**	1	82	94	90:10
4	4-FC$_6$H$_4$	**4d**	1	85	91	87:13
5	3-ClC$_6$H$_4$	**4e**	1	92	92	91:9
6	4-ClC$_6$H$_4$	**4f**	1	95	92	89:11
7	3-BrC$_6$H$_4$	**4g**	1	89	88	90:10
8	4-BrC$_6$H$_4$	**4h**	1	91	90	93:7
9	3-MeC$_6$H$_4$	**4i**	1	92	90	92:8
10	4-MeC$_6$H$_4$	**4j**	1	95	92	92:8
11	2-naphthyl	**4k**	1	94	95	96:4
12	*n*Pr	**4l**	1	80	94	86:14

[a] Unless otherwise noted, all reactions were carried out with **1c·HBAr$^{F}_{4}$** (5 mol%), 4 Å MS (20 mg), NBS (0.11 mmol) and **2** (0.1 mmol) in CH_2Cl_2 (0.15 mL) at −20°C. [b] Isolated yield. [c] Determined by HPLC. [d] Determined by ^{1}H NMR spectroscopy and HPLC analysis. [e] Trace amount of aza-Michael product was observed.

resolution.[11] It is interesting to note that this process could be accelerated by strong inorganic and organic bases, such as KOH, NaOH, KO*t*Bu, and tetramethyl guanidine (TMG). The *cis* isomer (2*R*,3*S*)-**4a** was obtained in 89% yield, 93% *ee*, and 95:5 d.r. after treatment with KOH in toluene for 1 h (Scheme 2). The nature of the solvent had a significant effect on the epimerization (see the Supporting Information for details).[12] The stereochemistry at the 2-position of **4a** was maintained. We postulate that the transformation proceeds through an S_E1 mechanism with the *cis* diastereomer being the most thermodynamically stable product.



Scheme 2. The epimerization of *trans*-3-bromo-2,3-dihydroquinolin-4-one **4a**.

These results improve upon the existing substrate scope of enantioselective aza-Michael reaction and utilizes a one-pot protocol to access to 3-bromo-2,3-dihydroquinolin-4-one derivatives under mild reaction conditions. However, it is premature to advance a discrete model to rationalize the observed trends in stereoselectivity and the effect of temperature effects in the two processes. Nevertheless, we propose

that one guanidine–amide moiety activates the substrate through hydrogen-bonding interactions, and the other guanidium functional group, in conjuction with the counterion, provides a steric variation that is crucial in defining the size and shape of the substrate binding pocket.

In summary, we have developed a highly efficient bisguanidium organocatalyst for an intramolecular aza-Michael reaction and a one-pot bromination reaction, affording a series of optically enriched, 2-substituted dihydroquinones and brominated dihydroquinones (up to 99% yield and 99% *ee* for the aza-Michael reaction; and up to 95% yield, 96:4 d.r., and 95% *ee* for the one-pot bromination reaction). Both 2-aryl- and 2-alkyl-substituted products could be generated with excellent outcomes. Further studies into the reaction mechanism are currently in progress.

Experimental Section

Typical procedure for the asymmetric intramolecular aza-Michael reaction: Bisguanidium salt catalyst **1c·HBAr$^{F}_{4}$** (5 mol%, 4.3 mg) and substrate **2a** (23.8 mg, 0.05 mmol) were stirred in a dry reaction tube at −60 °C for 0.5 h. Subsequently, CH_2Cl_2(0.5 mL; cooled at −60 °C) was added. The reaction was stirred at −60 °C and monitored by TLC. After complete consumption of the starting materials, the mixture was directly purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 8:1) to afford **3a** (23.6 mg, 99% yield) as a light yellow solid.

Typical procedure for the asymmetric one-pot bromination reaction: Bisguanidium salt catalyst **1c·HBAr$^{F}_{4}$** (5 mol%, 8.6 mg), 4 Å molecular sieves (20 mg), *N*-bromosuccinimide (NBS; 19.6 mg, 0.11 mmol) and substrate **2a** (47.7 mg, 0.1 mmol) were stirred in a dry reaction tube at −20 °C for 0.5 h. Subsequently, CH_2Cl_2 (0.15 mL; cooled at −20 °C) was added. The reaction was stirred at −20 °C for 24 h. The mixture was directly purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 8:1) to afford **4a** (48.8 mg, 88% yield) as a white solid.

Acknowledgements

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Keywords: asymmetric synthesis · bromination · dihydroquinolones · guanidines · Michael addition

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[5] CCDC-897037 (**2f**), 892342 (**4a**) and 892841 (**5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[12] The aza-Michael product **3a** was detected when CH_3CN was used as the solvent. Complicated side products were generated when **4a** was treated with KOH in methanol.

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