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ENANTIOSELECTIVE SYNTHESIS OF 2-ARYL-2,3-DIHYDRO-4-QUINOLONES BY CHIRAL BRØNSTED ACID CATALYZED INTRAMOLECULAR AZA-MICHAEL ADDITION REACTION

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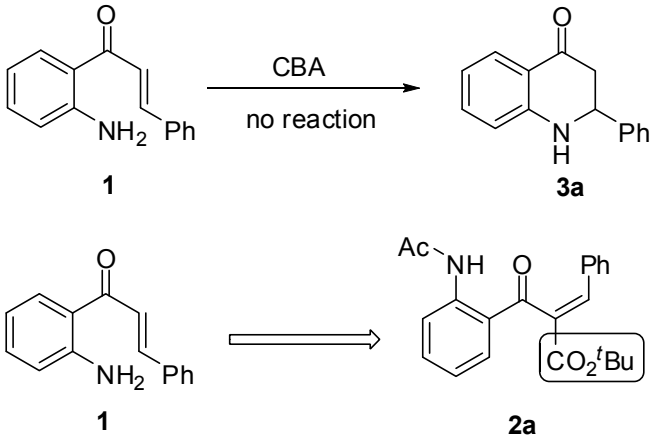
Abstract – Asymmetric intramolecular aza-Michael addition of activated α,β-unsaturated ketones catalyzed by chiral *N*-triflyl phosphoramide was realized. Enantioenriched 2-aryl-2,3-dihydroquinolin-4-ones can be obtained in excellent yields (77-98%) with up to 82% ee.

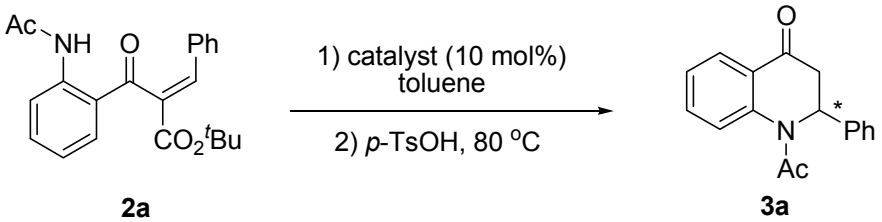
2-Aryl-2,3-dihydroquinolin-4-ones are a class of heterocyclic compounds with significantly biological importance.[1-3] Consequently, enormous synthetic efforts have been devoted to their efficient synthesis.[4-9] Despite the recent progress towards the synthesis of 2-aryl-2,3-dihydroquinolin-4-ones, the catalytic enantioselective synthesis is rather limited. Notably, Hayashi and co-workers developed rhodium-catalyzed enantioselective 1,4-addition of arylzinc reagents to 4-quinolones, leading to optically pure 2-aryl-2,3-dihydro-4-quinolones.[10] More interestingly, during the studies on testing 2-aryl-2,3-dihydro-4-quinolones as a new class of antitumor agents,[1-2] their two enantiomers were found to display distinct activities. This difference in reactivity of two enantiomers together with only limited enantioselective synthesis has made that the development of efficient asymmetric catalytic synthesis of 2-aryl-2,3-dihydro-4-quinolones is urgent and highly desirable. As a straightforward synthesis, the route to 2-aryl-2,3-dihydro-4-quinolones by intramolecular aza-Michael addition of enone is very attractive. However, the catalytic asymmetric synthesis by this means is still unknown despite of the fact that the intermolecular aza-Michael addition of enone have been demonstrated efficiently by several groups.[11-15] As part of our ongoing program in exploring chiral Brønsted acid catalysis,[16-18] we recently realized the chiral Brønsted acid-catalyzed asymmetric intramolecular oxa-Michael addition of activated α,β-unsaturated ketones.[19] The flavanone products can be synthesized with excellent yields (50-95%)

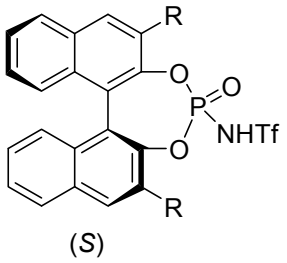
and up to 74% *ee* by chiral *N*-triflyl phosphoramide.[20-22] We then envisaged that chiral *N*-triflyl phosphoramide might be suitable for the aza-Michael addition of activated α,β-unsaturated ketones to afford the enantioenriched 2-aryl-2,3-dihydro-4-quinolones. In this paper, we report the preliminary study on this subject.



The initial testing of substrate **1** with chiral *N*-triflyl phosphoramide did not lead to the cyclization product. To increase the reactivity of enone, *tert*-butyl ester activated α,β-unsaturated ketone **2a** is employed as substrate, and the *tert*-butyl ester moiety can be removed after the cyclization.[23-24] To our delight, substrate **2a** underwent the cyclization in the presence of chiral *N*-triflyl phosphoramide smoothly. Several chiral *N*-triflyl phosphoramide catalysts have been tested, and the results are summarized in Table 1. All the tested chiral *N*-triflyl phosphoramides were able to catalyze this reaction smoothly with excellent yields. The best enantioselectivity (72% ee) was obtained when (*S*)-**4g**, catalyst bearing 1-naphthyl substituent, was used (entry 7, Table 1).

Table 1. Screening of catalysts for the intramolecular aza-Michael addition





4a: R = 3,5-$(CF_3)_2$-C_6H_3
4b: R = 9-anthryl
4c: R = 9-phenanthryl
4d: R = 2,4,6-(^{i}Pr)$_3$-C_6H_2
4e: R = $SiPh_3$
4f: R = 3,5-$(Me)_2$-C_6H_3
4g: R = 1-naphthyl
4h: R = 3,5-$(CF_3)_2$-$C_{12}H_7$

entry[a]	catalyst	T (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**4a**	60	48	90	11
2	**4b**	60	36	90	66
3	**4c**	60	12	91	50
4	**4d**	60	48	88	4
5	**4e**	80	48	86	30
6	**4f**	60	48	86	43
7	**4g**	60	48	95	72
8[d]	**4h**	60	48	97	60

[a] Reaction conditions: 10 mol% of (*S*)-**4**, 0.10 mol/L of **2a** in toluene.

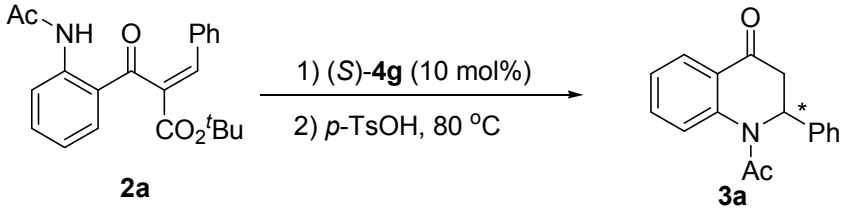
[b] Isolated yields.

[c] Determined by chiral HPLC analysis (Chiralpak AD-H).

[d] Without adding *p*-TsOH.

With 10 mol% of (*S*)-**4g**, *N*-Ac substrate **2a** was chosen to further optimize the reaction conditions. As summarized in Table 2, several commonly used solvents have been tested. Nonpolar solvents such as toluene, *p*-xylene and CCl_4 were all well tolerated, giving almost identical yields and ees. The optimized reaction condition was chosen as the following: 10 mol% (*S*)-**4g**, 60 ˚C, and toluene as the solvent.

Table 2. Influence of solvents on the intramolecular aza-Michael addition



2a **3a**

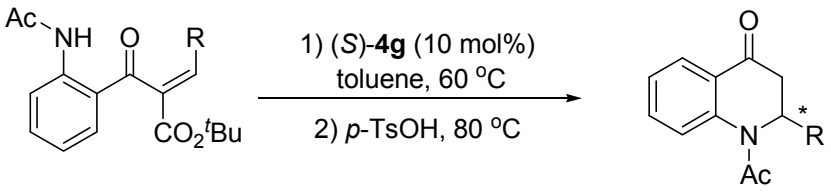
entry[a]	solvent	T (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	toluene	60	48	95	72
2	benzene	60	48	trace	-
3	*p*-xylene	60	36	94	72
4	Et_2O	reflux	48	-	-
5	CH_2Cl_2	reflux	48	-	-
6	DCE	60	48	trace	-
7	CCl_4	60	36	95	72

[a] Reaction conditions: 10 mol% of (*S*)-**4g**, 0.10 mol/L of **2a** in solvent.

[b] Isolated yields.

[c] Determined by chiral HPLC analysis (Chiralpak AD-H)

Table 3. Substrate scope of the intramolecular aza-Michael addition



2 **3**

entry[a]	**2**, R	**3**, yield (%)[b]	ee (%)[c]
1	**2a**, Ph	**3a**, 95	(-) 72
2	**2b**, 4-Br-C_6H_4	**3b**, 90	(-) 58 (S)[d]
3	**2c**, 4-Cl-C_6H_4	**3c**, 90	(-) 67
4	**2d**, 4-NO_2-C_6H_4	**3d**, 77	(-) 20
5	**2e**, 4-Me-C_6H_4	**3e**, 98	(-) 82
6	**2f**, 4-MeO-C_6H_4	**3f**, 94	(-) 60
7	**2g**, 2-MeO-C_6H_4	**3g**, 95	(+) 4
8	**2h**, 1-naphthyl	**3h**, 81	(+) 76
9	**2i**, 2-naphthyl	**3i**, 98	(-) 76

[a] Reaction conditions: 10 mol% of (*S*)-**4g**, 0.10 mol/L of **2** in toluene.

[b] Isolated yields.

[c] Determined by chiral HPLC analysis, and with the sign of the optical rotation.

[d] Absolute configuration was determined by X-ray analysis of enantiopure **3b**.

Under these optimized reaction condition, different substrates were explored to examine the generality of the reaction.[25] The results are summarized in Table 3. A variety of aryl groups could be accommodated in the reaction, and the corresponding products were obtained in high yields with moderate enantioselectivities (77-98% yields, 4-82% *ee*s). However, substrate **2d** bearing NO_2 led to the cyclization product in only 77% yield with a low ee (entry 4, Table 3). When the substrate **2g** with electron-donating group (MeO) at *ortho*-position was used, excellent yield could be obtained, but with only 4% *ee* (entry 7, Table 3). The *para*-tolyl substituted substrate **2e** gave the highest enantioselectivity (82% *ee*, entry 5, Table 3). The 1-naphthyl and 2-naphthyl substituted substrates gave the good enantioselectivity (76% *ee*, entries 8,9, Table 3).

In order to determine the absolute configuration of the products obtained here, the enantiopure **3b** was obtained preparative chiral HPLC separation. The crystal structure of enantiopure **3b** was obtained, and a single-crystal X-ray analysis determined its configuration as S (Figure 1).

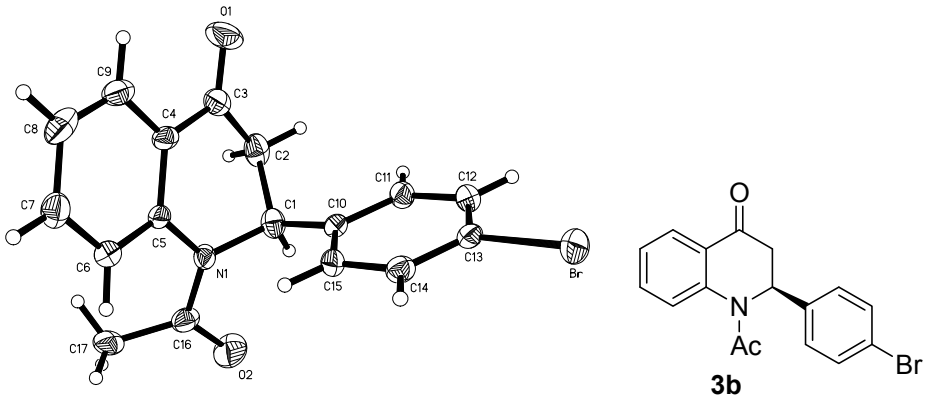


Figure 1. X-Ray structure of enantiopure (S)-**3b**. Ellipsoids at 30% probability

In summary, we have developed the asymmetric intramolecular aza-Michael addition of activated α,β-unsaturated ketones by utilizing chiral *N*-triflyl phosphoramide. The enantioenriched 2-aryl-2,3-dihydroquinolin-4-ones can be synthesized in excellent yields (77-98%) with up to 82% ee. Further tuning the catalyst to broaden the substrate scope is ongoing in the lab.

ACKNOWLEDGEMENTS

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25. Selected data for new compounds: **3g**: white solid, 95% yield, 4% ee, $[\alpha]_D^{20}$ +3.7° (c 0.30, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.19-3.35 (m, 2H), 3.84 (s, 3H), 6.30 (brs, 1H), 6.69 (t, *J* = 7.8 Hz, 1H), 6.84 (t, *J* = 8.1 Hz, 2H), 7.14-7.27 (m, 2H), 7.54 (t, *J* = 8.1 Hz, 1H), 7.68 (brs, 1H), 7.96 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 42.8, 52.9, 55.2, 110.6, 120.2, 124.8, 124.9, 125.8, 126.1, 127.0, 127.5, 129.0, 134.4, 142.7, 156.9, 170.0, 193.4; IR (film) 3002, 1683, 1664, 1653, 1600, 1479, 1461, 1365, 1317, 1292, 1255, 1228, 1211, 1109, 1033, 775, 758, 418 cm^{-1}; MS (EI): 295 (M^+, 27), 253 (38), 252 (100), 146 (51), 119 (22), 91 (23), 77 (12), 43 (22); HRMS (EI): Exact mass calcd for $C_{18}H_{17}NO_3$ $[M]^+$: 295.1208. Found: 295.1211. mp 198 - 200 °C. Chiral HPLC

analysis : Daicel Chiralpak AD-H (25 cm), Hexanes / IPA = 80 / 20, 0.6 mL/min, λ = 230 nm, t (major) = 26.89 min, t (minor) = 24.82 min. **3h**: white solid, 81% yield, 76% ee, $[\alpha]_D^{20}$ +8.9° (c 0.30, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.37-3.41 (m, 2H), 6.85 (brs, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 7.00-7.17 (m, 4H), 7.47-7.57 (m, 3H), 7.79 (d, *J* = 8.1 Hz, 1H), 8.00 (d, *J* = 7.5 Hz, 1H), 8.35 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0, 43.3, 52.1, 123.7, 124.4, 125.4, 125.8, 126.0, 126.4, 126.9, 127.0, 127.4, 128.7, 129.0, 131.4, 133.6, 133.7, 134.2, 141.7, 169.5, 194.5; IR (film) 3049, 2966, 1687, 1663, 1598, 1481, 1363, 1293, 1276, 1228, 794, 774, 539 cm^{-1}; MS (EI): 315 (M^+, 56), 273 (77), 272 (100), 154 (24), 153 (39), 152 (26), 146 (70), 141 (17), 128 (19), 90 (10), 43 (28); HRMS (EI): Exact mass calcd for $C_{21}H_{17}NO_2$ $[M]^+$: 315.1259. Found: 315.1260. mp 196 – 198 °C. Chiral HPLC analysis: Daicel Chiralpak AD-H (25 cm), Hexanes / IPA = 80 / 20, 0.6 mL/min, λ = 230 nm, t (major) = 15.12 min, t (minor) = 16.92 min. **3i**: white solid, 98% yield, 76% ee, $[\alpha]_D^{20}$ -76.1°(c 0.30, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.38-3.56 (m, 2H), 6.68 (brs, 1H), 7.10-7.54 (m, 7H), 7.69-7.72 (m, 3H), 7.92 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 42.3, 54.6, 124.9, 125.0, 125.6, 126.0, 126.2, 126.3, 127.2, 127.4, 127.9, 128.6, 132.4, 132.8, 134.4, 135.4, 141.6, 170.2, 193.2; IR (film) 1664, 1601, 1480, 1459, 1379, 1379, 1283, 1228, 1116, 1025, 862, 780, 477 cm^{-1}; MS (EI): 315 (M^+, 20), 273 (40), 272 (100), 154 (17), 146 (32), 43 (19); HRMS (EI): Exact mass calcd for $C_{21}H_{17}NO_2$ $[M]^+$: 315.1259. Found: 315.1262. mp: 154 – 156 °C. Chiral HPLC analysis : Daicel Chiralpak AD-H (25 cm), Hexanes / IPA = 80 / 20, 0.6 mL/min, λ = 230 nm, t (major) = 22.00 min, t (minor) = 25.48 min.