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STEREOSELECTIVE AZA-HENRY REACTION OF 3-NITRO-DIHYDRO-2(1*H*)-QUINOLONES WITH *N*-BOC-ALDIMINES UNDER THE CATALYSIS OF CHIRAL AMMONIUM BETAINES†

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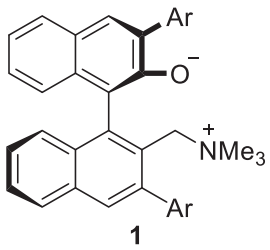
Abstract – A highly enantioselective aza-Henry reaction between 3-nitro-dihydro-2(1*H*)-quinolones and *N*-Boc-aldimines was developed by using a chiral ammonium betaine as a catalyst. This protocol provides a direct synthetic method for accessing hydroquinoline derivatives possessing a tetrasubstituted stereogenic center at the C3 position and casts light on the utility of the α-functionalization of dihydroquinolones.

Optically pure *N*-heterocyclic compounds constitute the common structural core of putative chemotherapeutics and natural products. Among them, hydroquinoline derivatives have attracted much attention owing to their prominent pharmaceutical activity.[1] In particular, dihydro-2(1*H*)-quinolones have emerged as valuable scaffolds for the assembly of stereochemically defined, chiral tetrahydroquinoline frameworks. The previously reported catalytic approaches towards the synthesis of chiral hydroquinolones mostly relied on the construction of the heterocyclic ring, possessing an enantiomerically enriched carbon atom at the C4-position, by means of asymmetric cyclizations.[2-5] Although the enantioselective α-functionalization of the carbonyl moiety of hydroquinolones could provide a direct method for the installation of a tetrasubstituted stereogenic center at the C3 position of this important class of heterocycles, this possibility remains unexplored and no catalytic systems are currently available for enabling this mode of bond formation with rigorous absolute stereocontrol.[6]

† Dedicated to Professor Dr. Masakatsu Shibasaki on the occasion of his 70th birthday

With this methodological deficiency in mind, we envisaged that C_1-symmetric chiral ammonium betaines of type **1** (Figure 1) could function as effective organic base catalysts for facilitating the enolization of hydroquinolones, bearing a suitable electron-withdrawing functionality at the carbonyl α-carbon, and the subsequent stereoselective bond formations. This hypothesis was based on the consideration of the ability of the conjugate acids of **1** to precisely recognize and control reactive enolates through cooperative hydrogen-bonding and ionic interactions.[7-11] Herein, we report the development of the first highly stereoselective aza-Henry reaction between 3-nitro-dihydro-2(1*H*)-quinolones **2** and *N*-Boc-aldimines **3** under the catalysis of **1**.[12-14]



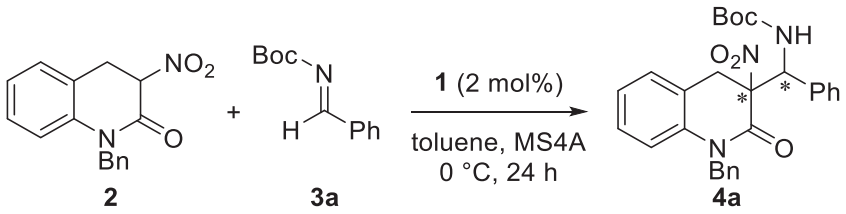
1

1a: Ar = Ph
1b: Ar = 4-^{t}BuC$_6$H$_4$
1c: Ar = 3,5-^{t}Bu$_2$C$_6$H$_3$
1d: Ar = 2,4,6-Me$_3$C$_6$H$_2$
1e: Ar = 4-CF$_3$C$_6$H$_4$
1f: Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$

Figure 1. Chiral Ammonium Betaines

Initial investigation was carried out by treating *N*-benzyl-3-nitro-dihydro-2(1*H*)-quinolone (**2a**) with *N*-Boc-benzaldimine (**3a**) in toluene at 0 °C in the presence of chiral ammonium betaine **1a** (2 mol%) and molecular sieves 4 Å (MS4A)[15] (Table 1, entry 1). The reaction proceeded smoothly to give the desired aza-Henry adduct **4a** as a mixture of diastereomers in a 1.8:1 ratio, as determined by 600 MHz ^{1}H NMR analysis of a crude aliquot. After standard silica gel column chromatography, **4a** was isolated in 91% yield, and the enantiomeric excess (ee) of the two diastereomers was revealed to be 92 and 90%, respectively, by chiral HPLC analysis. Encouraged by these promising results, we next evaluated the effect of the catalyst structure on the reactivity and selectivity. While an increase in the steric demand of the 3,3'-substituents of **1** led to a considerable decrease in the catalytic activity and stereocontrolling ability (entries 2-4), the introduction of electron-deficient aromatic appendages, particularly a 3,5-bis(trifluoromethyl)phenyl group (**1f**), delivered a marked improvement in both diastereo- and enantioselectivity (entries 5 and 6). It should be noted that the catalyst loading could be reduced to 1 mol% without compromising the reaction efficiency and stereoselectivity by conducting the reaction at a higher substrate concentration (0.2 M with respect to **2**) (entry 7).

Table 1. Catalyst Optimization[a]

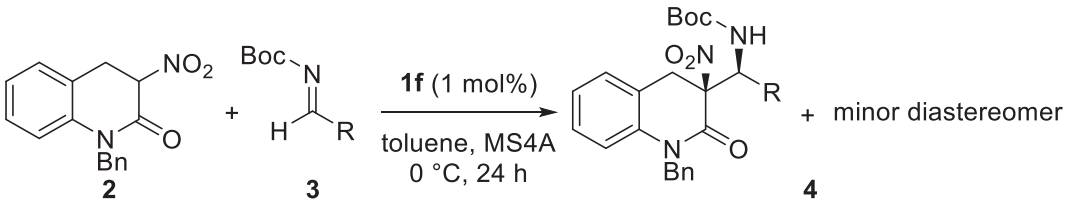


entry	**1**	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a** (Ar = Ph)	91	1.8:1	92/90
2	**1b** (Ar = 4-^{t}BuC$_6$H$_4$)	94	1.4:1	90/86
3	**1c** (Ar = 3,5-^{t}Bu$_2$C$_6$H$_3$)	63	1:1.4	38/2.3
4	**1d** (Ar = 2,4,6-Me$_3$C$_6$H$_2$)	68	1:1.6	29/39
5	**1e** (Ar = 4-CF$_3$C$_6$H$_4$)	96	2.3:1	98/96
6	**1f** (Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$)	88	6.5:1	99/93
7[e]	**1f**	99	6.6:1	99/92

[a] Unless otherwise noted, the reaction was performed with 0.1 mmol of **2a**, 0.11 mmol of **3a**, and 2 mol% of **1** in toluene (1.0 mL) with MS4A (100 mg) at 0 °C. [b] Isolated yield. [c] Diastereomeric ratios were determined by 600 MHz ^{1}H NMR analysis of crude aliquots. [d] Enantiomeric excesses were analyzed by chiral stationary phase HPLC. Relative and absolute configurations of **4a** was assigned as analogy to **4f** (*vide infra*). [e] 1 mol% of **1f** was used in 1.0 mL of toluene on 0.2 mmol scale.

Optimal catalyst **1f** and reaction conditions were then used for probing the scope of *N*-Boc-aldimine **3** (Table 2). With substituted benzaldehyde-derived *N*-Boc-imines **3b**-**3h**, an excellent enantioselectivity was consistently observed irrespective of their steric and electronic properties, while the diastereoselectivity was generally moderate (entries 1-7). Although a nearly complete enantiocontrol was feasible, a higher catalyst loading was required for ensuring the satisfactory conversion of *N*-Boc-2-naphthaldimine **3i** (entry 8). A relatively high level of diastereoselectivity was attained in the reaction with imine **3j** derived from 3-thiophenecarboxaldehyde and the corresponding aza-Henry adduct **4j** was obtained in an almost enantiomerically pure form (entry 9). When aliphatic *N*-Boc-aldimines were employed as electrophiles, a substantial erosion of reactivity and stereoselectivity was inevitable (entries 10 and 11). The absolute and relative configurations of major diastereomer of the aza-Henry adduct **4f** were unambiguously determined by single-crystal X-ray diffraction analysis as shown in Figure 2, and the stereochemistry of the remaining examples was assumed to be analogous.

Table 2. Substrate Generality[a]



entry	R (**3**)	yield (%)[b]	dr[c]	ee (%)[d]	**prod.**
1	4-$MeOC_6H_4$ (**3b**)	99	7.8:1	98/88	**4b**
2	4-MeC_6H_4 (**3c**)	90	5.5:1	98/89	**4c**
3	4-ClC_6H_4 (**3d**)	96	6.7:1	99/94	**4d**
4[e]	3-$MeOC_6H_4$ (**3e**)	95	5.1:1	99/93	**4e**
5	3-BrC_6H_4 (**3f**)	99	4.0:1	94/87	**4f**
6	2-MeC_6H_4 (**3g**)	73	2.4:1	96/93	**4g**
7	2-FC_6H_4 (**3h**)	99	4.3:1	99/98	**4h**
8[e]	2-naphthyl (**3i**)	99	6.5:1	98/93	**4i**
9	3-thiophenyl (**3j**)	99	11:1	99/93	**4j**
10	Me_2CHCH_2 (**3k**)	84	1.5:1	57/41	**4k**
11	$Me(CH_2)_7$ (**3l**)	76	1.9:1	59/41	**4l**

[a] The reaction was performed with 0.2 mmol of **2**, 0.22 mmol of **3**, and 1 mol% of **1f** in toluene (1.0 mL) with MS4A (100 mg) at 0 °C. [b] Isolated yield. [c] Diastereomeric ratios were determined by 600 MHz ^{1}H NMR analysis of crude aliquots. [d] Enantiomeric excesses were analyzed by chiral stationary phase HPLC. Relative and absolute configurations of **4f** were determined by X-ray crystallographic analysis and those of other **4** were assigned by analogy (see Figure 2). [e] 2 mol% of **1f** was used.

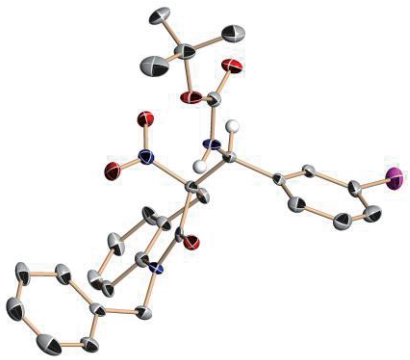


Figure 2. ORTEP diagram of major diastereomer of **4f** (Ellipsoids displayed at 50% probability. Solvent molecule and calculated hydrogen atoms except for them attached to stereogenic carbon are omitted for clarity. Gray: carbon, red: oxygen, blue: nitrogen, pink: bromine.)

In summary, we have developed a highly enantioselective aza-Henry reaction between 3-nitro-dihydro-2(1*H*)-quinolones and *N*-Boc-aldimines under the catalysis of chiral ammonium betaines. This unprecedented protocol offers a convenient access to useful precursors of optically active tetrahydroquinolines, the privileged structural motif found in biologically relevant molecules, and would stimulate the further development of novel asymmetric transformations of dihydro-2(1*H*)-quinolones.

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15. The addition of MS4A is crucial for attaining reproducibility and high enantioselectivity probably because a small amount (<5%) of water from slightly hygroscopic **1** would be incorporated into a

hydrogen-bonding network in the transition state, causing a substantial decrease in enantioselectivity. The reaction between **2a** and **3a** with **1a** as a catalyst in the absence of MS4A afforded the adduct **4a** in 98% yield with diastereomeric ratio of 1.2:1 and the enantiomeric excesses were determined to be 79/55%, respectively.