Bifunctional thiourea-promoted cascade aza-Michael-Henry-dehydration reactions: asymmetric preparation of 3-nitro-1,2-dihydroquinolines†

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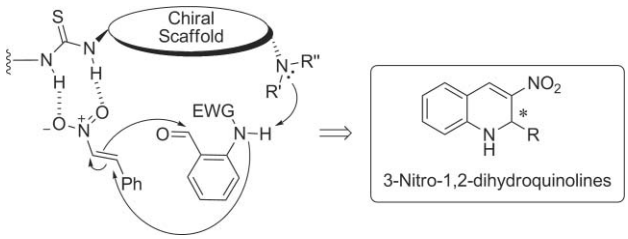
A cascade aza-Michael-Henry-dehydration reaction catalyzed by quinidine-derived tertiary amine-thiourea catalyst was developed *via* installation of suitable electron withdrawing groups at the amino function of aniline. This strategy led to a one-step preparation of chiral 3-nitro-1,2-dihydroquinolines in high yields and with up to 90% enantiomeric excesses.

Hydroquinolines, which possess a broad spectrum of biological activities, are of great importance in pharmaceutical industry and medicinal chemistry.[1] In particular, functionalized 1,2-dihydroquinolines are useful structural motifs and synthetic intermediates in natural product synthesis.[1a,1d] Methods for the catalytic asymmetric synthesis of chiral 1,2-dihydroquinolines are very limited.[2] Shibasaki and co-workers developed an asymmetric Reissert-type reaction promoted by a Lewis acid–Lewis base bifunctional catalyst to access chiral 2-cyano-1,2-dihydroquinolines.[3] Wang *et al.* disclosed an asymmetric synthesis of 3-formyl-1,2-dihydroquinolines employing a domino conjugate addition-aldol-dehydration reaction promoted by prolinol silyl ether *via* an iminium-enamine activation.[4] A similar approach for the dihydroquinoline synthesis was independently reported by Córdova and co-workers.[5] Given the importance of functionalized 1,2-dihydroquinoline compounds, and lack of efficient method for the preparation of chiral 3-nitro-1,2-dihydroquinolines,[6] we set out to develop an organocatalytic approach to tackle this synthetic challenge.

Bifunctional organic molecules containing a tertiary amino group and a thiourea moiety have been established as remarkably useful organic catalysts.[7] We envisage that a cascade process[8] mediated by tertiary amine-thiourea catalyst may lead to a one-pot generation of chiral 3-nitro-1,2-dihydroquinoline (Scheme 1). Installation of an electron-withdrawing group on the amino moiety of 2-aminobenzaldehyde is anticipated to increase the aniline N–H acidity, and the abstraction of which by the tertiary amine leads to an aza-Michael reaction. The thiourea group in the chiral catalyst is anticipated to have hydrogen bonding interactions with the nitro group. The subsequent Henry reaction with the aldehyde, followed by dehydration is expected to generate 3-nitro-1,2-dihydroquinoline.

To test the above hypothesis, a sulfonyl was used to activate the amino group, and the reaction between *N*-(2-formylphenyl)benzenesulfonamide and nitrooelfin was chosen for initial exploration. As cinchona alkaloids are well-established organic catalysts,[9] a number of cinchona alkaloid-based organocatalysts were examined in our study (Table 1). To our delight, quinine-derived **4** and quinidine **5** effectively promoted the projected cascade reactions, yielding the desired 3-nitro-1,2-quinolines in excellent yields, albeit with poor enantioselectivities (entries 1 and 2). Quinidine-derived sulfonamide[10] **6** was completely ineffective (entry 3). While quinidine-derived thiourea catalysts **7**, **8** and **9** offered low enantioselectivities (entries 4–6), thiourea **10** was found to be a good catalyst, affording the desired quinoline in moderate enantioselectivity (entry 7). Enantioselectivity was substantially improved when toluene was used as a solvent (entry 8). Electron-withdrawing sulfone group in the sulfonamide substrate is essential for the observed reactivity, as no reaction was observed when 2-aminobenzaldehyde or its *N*-Cbz-protected derivative was used.[11] We reasoned that the sulfonamide moiety in the substrate might play an important role in asymmetric induction, thus various sulfonamides were prepared and their influences on the reactions were investigated. Methanesulfonyl group afforded the product in high yield, but the enantioselectivity was significantly decreased, suggesting that the steric hindrance of the sulfonamide may be important in the asymmetric induction (entry 9). Sulfonamides containing various electron-withdrawing groups on the phenyl rings or naphthylene gave results comparable to those obtained with tosylsulfonamide (entries 10 to 13). By employing sterically hindered 2,4,6-trimethylbenzenesulfonamide substrate, very good enantioselectivity was attainable (entry 14). Using more hindered 2,4,6-triisopropylbenzenesulfonamide led to further improvement in the enantioselectivity of the reaction. Under the optimized reaction conditions, the desired 3-nitro-1,2-dihydroquinoline was obtained in 81% yield and with 90% ee (entry 16).

This cascade aza-Michael-Henry-dehydration reaction is applicable to different nitroolefins (Table 2). Various *meta*- or *para*-substituted aryl nitroolefins were suitable substrates, and the electronic nature of the aromatic rings can be varied. In addition, aliphatic nitroolefin could be used. Moreover, employment of



Scheme 1 Synthesis of 3-nitro-1,2-dihydroquinoline *via* a cascade aza-Michael-Henry-dehydration reaction.

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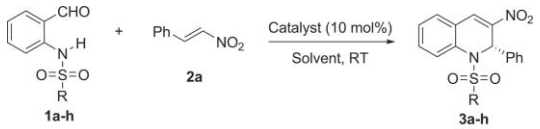
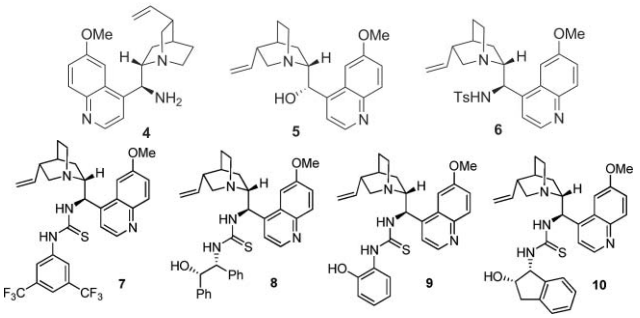
† Electronic supplementary information (ESI) available: Experimental details, analytic data, HPLC chromatogram and NMR spectra of the products. See DOI: 10.1039/c0ob00223b

Table 1 Screening of organic catalysts for cascade aza-Michael-Henry-dehydration reaction[a]



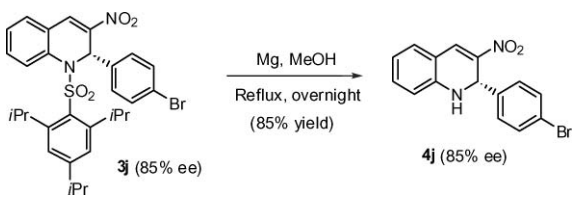


Entry	Cat.	R	Solvent	*t*/h	Yield[b] (%)	ee[c] (%)
1	**4**	*p*CH_3–Ph	CH_2Cl_2	12	95	13
2	**5**	*p*CH_3–Ph	CH_2Cl_2	48	95	12
3	**6**	*p*CH_3–Ph	CH_2Cl_2	73	—	—
4	**7**	*p*CH_3–Ph	CH_2Cl_2	24	95	23
5	**8**	*p*CH_3–Ph	CH_2Cl_2	48	70	15
6	**9**	*p*CH_3–Ph	CH_2Cl_2	50	80	9
7	**10**	*p*CH_3–Ph	CH_2Cl_2	50	95	48
8	**10**	*p*CH_3–Ph	Toluene	72	95	70
9	**10**	CH_3	Toluene	48	95	40
10	**10**	*p*CF_3–Ph	Toluene	72	43	63
11	**10**	*p*NO_2–Ph	Toluene	72	79	58
12	**10**	3,5-CF_3–Ph	Toluene	18	> 95	55
13	**10**	1-naphthyl	Toluene	72	> 95	72
14	**10**	2,4,6-Me–Ph	Toluene	60	80	86
15	**10**	2,4,6-*i*Pr–Ph	Toluene	60	57	90
16[d]	**10**	2,4,6-*i*Pr–Ph	Toluene	**72**	**81**	**90**
17	**10**	2,4,6-*i*Pr–Ph	CH_2Cl_2	72	60	65
18	**10**	2,4,6-*i*Pr–Ph	Xylene	72	70	86
19	**10**	2,4,6-*i*Pr–Ph	DMF	48	95	0

[a] The reactions were performed with **1** (0.025 mmol), **2a** (0.075 mmol) and the catalyst (0.0025 mmol) in anhydrous solvent (0.2 mL) at room temperature, unless otherwise specified; [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis. [d] 20 mol% catalyst was used.

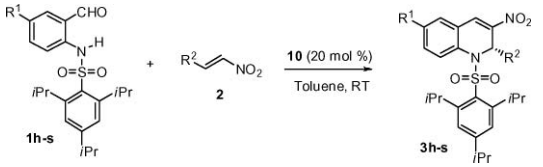
different *ortho*-formyl anilines led to the ready formation of different quinolines. However, *ortho*-substituted aryl nitroolefins were poor substrates,[12] likely due to the steric repulsion resulted from the nearby bulky sulfonamide group.

The sulfonyl group could be easily removed by reductive cleavage. When **3j** was treated with magnesium in methanol under refluxing condition, 2-aryl-substituted 3-nitro-1,2-dihydroquinoline **4j** was obtained in good yield. It should be noted that the enantioselectivity was maintained and the bromine atom on the benzene ring was not affected (Scheme 2).



Scheme 2 Reductive removal of the sulfonyl group

Table 2 Asymmetric synthesis of various 3-nitro-1,2-dihydroquinolines *via* **10**-promoted cascade aza-Michael-Henry-dehydration reaction[a]



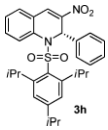
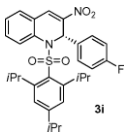
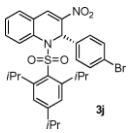
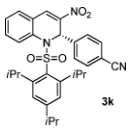
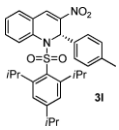
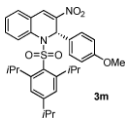
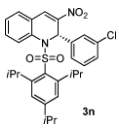
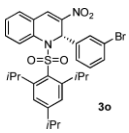
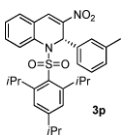
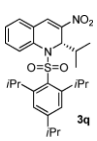
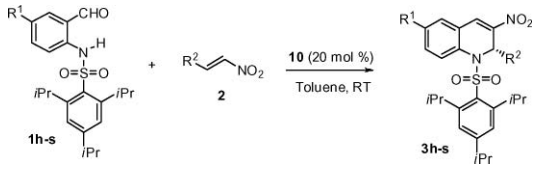
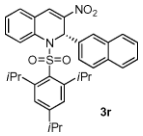
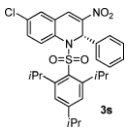
Entry	Product	*t*/h	Yield[b] (%)	ee[c] (%)
1	 **3h**	72	81	90
2	 **3i**	36	77	82
3	 **3j**	36	91	85
4	 **3k**	36	92	87
5	 **3l**	48	83	81
6	 **3m**	48	75	84
7	 **3n**	72	90	87
8	 **3o**	72	86	89
9	 **3p**	72	83	81
10	 **3q**	72	86	70

Table 2 *(Contd.)*



Entry	Product	*t*/h	Yield[b](%)	ee[c](%)
11[d]		72	75	82
12		72	78	88

[a] The reactions were performed with **1** (0.025 mmol), **2** (0.075 mmol) and **10** (0.0025 mmol) in anhydrous toluene (0.5 mL) at room temperature; [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis. [d] 50 mol% catalyst was used.

In conclusion, we have developed a new catalytic cascade aza-Michael-Henry-dehydration process for the efficient preparation of chiral 3-nitro-1,2-quinolines. Installing an electron-withdrawing sulfone group on anilines allows for their activation by well-established tertiary amine-thiourea catalysts, and this strategy may find wide applications in the preparation of nitrogen-containing heterocycles. Mechanistic understanding of this cascade reaction, development of other organocatalytic cascade processes and their applications to the asymmetric synthesis of flavonoids and their structural analogues are currently under investigation in our laboratory.

Acknowledgements

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11 2-Aminobenzaldehyde or benzyl 2-formylphenylcarbamate was mixed with catalyst **10** in toluene for 72 h, no reaction occurred.

12 When (*E*)-1-chloro-2-(2-nitrovinyl)benzene was subjected to the same reaction conditions, the corresponding quinoline was obtained in 60% yield and with 17% ee.