ORGANIC LETTERS

2010
Vol. 12, No. 23
5592−5595

Asymmetric Synthesis of 2-Aryl-2,3-dihydro-4-quinolones via Bifunctional Thiourea-Mediated Intramolecular Cyclization

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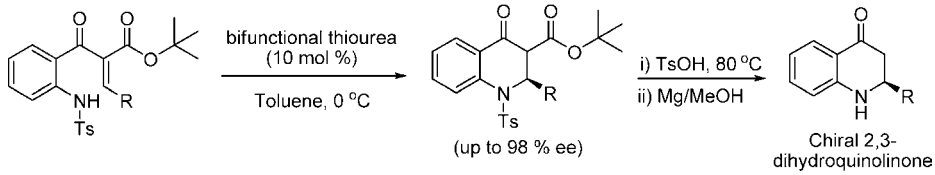
Received October 18, 2010

ABSTRACT



A novel asymmetric preparation of optically enriched 2-aryl-2,3-dihydroquinolin-4(1H)-ones has been developed. By installing a sulfonyl group on the nitrogen of the anilines and an ester function on the unsaturated ketones, an intramolecular organocatalytic cyclization took place readily in a stereoselective manner, resulting in the formation of dihydroquinolones with high enantioselectivity.

The quinolones are a family of compounds with broad-spectrum antibiotic properties.[1] In particular, 2-aryl-2,3-dihydro-4-quinolones represent a new class of antitumor agents.[2] Since individual stereoisomers of quinolones displayed different biological acitivities, it is highly desirable to develop enantioselective routes to access this class of important antibiotics. To the best of our knowledge, only two examples have been reported in the literature, both making use of transition metal-mediated catalytic processes. Hayashi and co-workers reported an asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones via a rhodium-catalyzed 1,4-addition of arylzinc reagent to 4-quinolones.[3] Recently, Hou et al. disclosed a kinetic resolution of 2,3-dihydro-2-substituted 4-quinolones by a palladium-catalyzed asymmetric allylic alkylation, affording chiral 2,3-disubstituted 2,3-dihydro-4-quinolones in excellent enantioselectivity.[4] Given the biological importance of 2-aryl-2,3-dihydro-4-quinolones, we were interested in developing organocatalytic synthetic methods for the practical preparation of these valuable molecules.

For a stereoselective synthesis of 2-aryl-2,3-dihydro-4-quinolones, an intramolecular conjugate addition of aniline to a properly activated alkene moiety appears to be an attractive strategy (Figure 1). The key issue here is how to effect the cyclization in an efficient and stereocontrolled manner. We recently reported a bifunctional thiourea-promoted cascade aza-Michael-Henry-dehydration reaction for the asymmetric preparation of 3-nitro-1,2-dihydroquinolines,[5] in which the nitrogen nucleophiles were activatived by installing a sulfonyl group. Thus, we envisioned that a sufonyl substituted aniline could be used as the nucleophilic component; in the presence of bifunctional tertiary amine-

(1) Wagman, A. S.; Wentland, M. P. In *Comprehensive Medicinal Chemistry II*; Taylor, J. B., Triggle, D. J., Eds.; Elsevier: Amsterdam, 2006; Vol. 7, pp 567−596.

(2) (a) Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Tachibana, Y.; Kuo, S.-C.; Hamel, E.; Hackl, T.; Lee, K.-H. *J. Med. Chem.* **1998**, *41*, 1155. (b) Zhang, S.-X.; Feng, J.; Kuo, S.-C.; Brossi, A.; Hamel, E.; Tropsha, A.; Lee, K.-H. *J. Med. Chem.* **2000**, *43*, 167.

(3) Shintani, R.; Yamagami, T.; Kimura, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 5317.

(4) Lei, B.-L.; Ding, C.-H.; Yang, X.-F.; Wan, X.-L.; Hou, X.-L. *J. Am. Chem. Soc.* **2009**, *131*, 18250.

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10.1021/ol102519z
Published on Web 11/03/2010

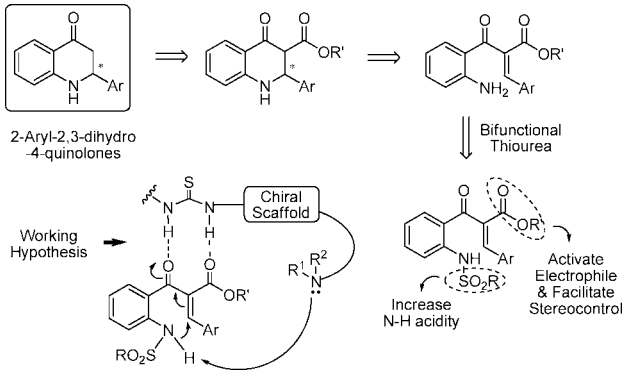


Figure 1. Preparation of of 2-aryl-2,3-dihydro-4-quinolones via an intramolecular cyclization reaction.

thiourea catalysts,[6] the acidic proton of the sulfonamide can be readily removed, initiating the subsequent intramolecular cyclization reaction. To better activate the electrophiles, an ester group could be installed at the α-position of the carbonyl function.[7] Such an ester group is expected to facilitate hydrogen bonding interactions between the substrates and the thiourea catalysts, leading to a better stereochemical control. With the established protocols for its decarboxylative cleavage,[7] the ester group can be readily removed at the end of the synthesis, without affecting the integrity of the newly created stereogenic center at the 2-position of chiral quinolones.

To prove the validity of our proposed synthetic strategy, alkylidene *β*-ketoester **4a** with a properly installed neighboring sulfonamide group was treated with catalyst **1** (Figure 2). To our delight, the intramolecular cyclization occurred smoothly to yield product **5a** in quantitative yield and with 87% ee. The next step is the cleavage of the ester group. Upon further treatment with TsOH at the elevated temperature, the decarboxylation[8] took place readily, and 2-phenyl-2,3-dihydro-4-quinolone **6a** was obtained in excellent yield and with 87% ee (Scheme 1).[9]

(6) For reviews, see: (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (b) Connon, S. J. *Chem. Commun.* **2008**, 2499. (c) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (d) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (e) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (f) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. For selective examples, see: (g) Zhu, Q.; Lu, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 7753. (h) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (i) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (j) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366. (k) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293. (l) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (m) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967. (n) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (o) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481.

(7) For a catalytic enantioselective synthesis of flavanones and chromanones, see: Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830.

(8) For reviews and selective examples for asymmetric decarboxylation reactions, see: (a) Blanchet, J.; Baudoux, J.; Amere, M.; Lasne, M.-C.; Rouden, J. *Eur. J. Org. Chem.* **2008**, *73*, 5493. (b) Brunner, H.; Baur, M. A. *Eur. J. Org. Chem.* **2003**, *68*, 2854. (c) Kukula, P.; Matousek, V.; Mallat, T.; Baiker, A. *Tetrahedron: Asymmetry* **2007**, *18*, 2859. (d) Detalle, J. F.; Riahi, A.; Steinmetz, V.; Henin, F.; Muzart, J. *J. Org. Chem.* **2004**, *69*, 6528. (e) Roy, O.; Diekmann, M.; Riahi, A.; Henin, F.; Muzart, J. *Chem. Commun.* **2001**, 533.

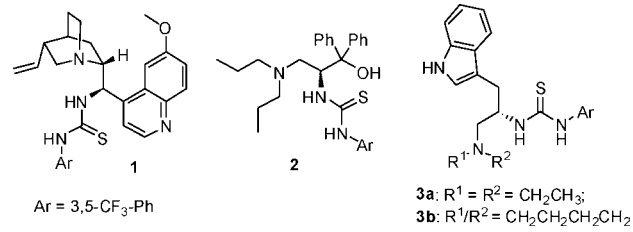
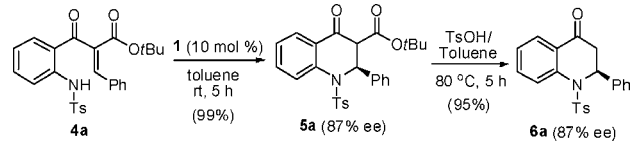


Figure 2. Bifunctional tertiary amine-thiourea catalysts employed in the study.

Scheme 1. Synthesis of 2-Phenyl-2,3-dihydro-4-quinolone **6a** via Conjugate Addition-Decarboxylation Sequence



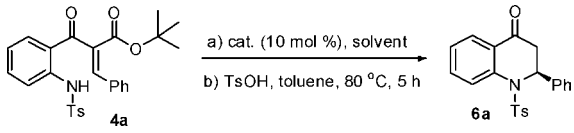
The enantiomeric purity of the final quinolone products is determined by the stereochemical outcome of the first intramolecular cyclization step, as the second decarboxylation step will not compromise the stereogenic integrity of the quinolone intermediates created. We therefore investigated the catalytic effects of various bifunctional catalysts (Figure 2) and explored different reaction conditions for the intramolecular conjugate addition step, aiming to improve the enantioselectivity of the process. L-Threonine-derived **2**, and L-tryptophan-based bifunctional catalysts **3a**[10] and **3b** all could promote the reactions; however, the desired products were obtained with disappointing enantioselectivity (Table 1, entries 2−4). A solvent screening revealed that toluene was the best reaction medium. By lowering the reaction temperature to 0 °C, the desired quinolone **6a** could be obtained in high yield and with 94% ee (entry 12). The sulfonyl group on the nitrogen was crucial, employment of alkylidene *β*-ketoester with the free amino group resulted in formation of the product with only 78% ee, comparing to a 94% ee under otherwise same reaction conditions.

The reaction scope was next studied, various alkylidene *β*-ketoesters with different substituents were examined, and the results are summarized in Table 2. It was found that *para*- or *meta*- substituted aromatic rings, regardless their electronic nature, were well-tolerated for the reaction. In all the examples examined, good yields and excellent enantioselectivities were obtained (entries 1−6). For the alkene bearing an *ortho*-methyl-phenyl substituent, the desired product could still be obtained in good yield and with excellent enantioselectivity, although much longer reaction was required (entry

(9) Alternatively, this two-step reaction sequence could be carried out without isolating the intermediates. However, we opted to perform the two steps separately since compounds **4** and **6** tend to have very similar polarity.

(10) Han, X.; Kwiatkowski, J.; Xue, F.; Huang, K.-W.; Lu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 7604.

Table 1. Catalyst Screening for the Synthesis of Quinolones via an Intramolecular Cyclization-Decarboxylation Sequence[a]



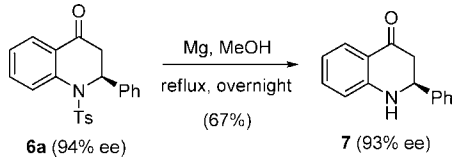
entry	cat.	solvent	t^b (h)	temp (°C)	yield[c] (%)	ee[d] (%)
1	**1**	Toluene	5	rt	99/95	87
2	**2**	Toluene	72	rt	79/89	11
3	**3a**	Toluene	24	rt	99/95	57
4	**3b**	Toluene	12	rt	99/95	20
5	**1**	MeOH	9	rt	99/95	35
6	**1**	CH_2Cl_2	51	rt	99/95	79
7	**1**	Hexane	72	rt	<30	–[e]
8	**1**	EtOAc	3	rt	99/95	42
9	**1**	THF	51	rt	99/95	36
10	**1**	CH_3CN	5	rt	99/91	73
11	**1**	Acetone	5	rt	99/95	42
12	**1**	Toluene	28	0	92/91	94

[a] Reactions were performed with **4a** (0.05 mmol) and catalyst (0.005 mmol) in anhydrous toluene (0.2 mL) at the temperature specified. [b] Time for step a. [c] Isolated yields for both steps. [d] ee value was determined by HPLC analysis on a chiral stationary phase. [e] Not determined.

7). 2-Naphthyl-substituted alkylidene could also be employed, and high ee was attainable (entry 8). When the alkyl substituent was used, the final 2-*i*Pr-2,3-dihydro-4-quinolone was prepared with 78% ee (entry 9).

The reductive cleavage of the sulfonyl protection was demonstrated in Scheme 2.[11] When **6a** (94% ee) was treated with magnesium in methanol at the refluxing condition, the desulfonated 2,3-dihydro-2-aryl-quinolin-4(1H)-one **7** with 93% ee was obtained.

Scheme 2. Cleavage of the *N*-Sulfonyl Group

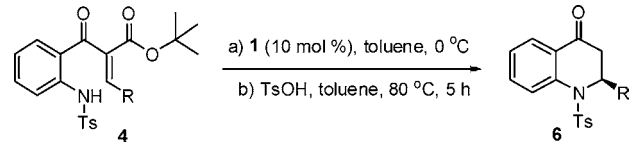


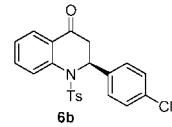
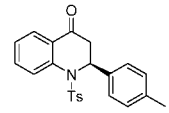
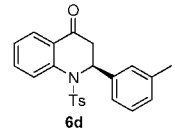
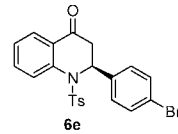
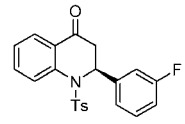
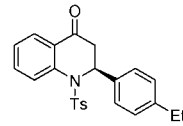
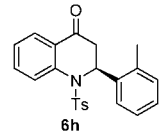
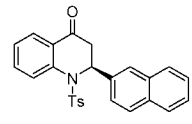
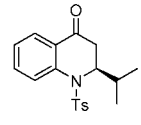
To account for the stereochemical outcome, a transition state model is proposed and shown in Figure 3. The thiourea moiety in the catalyst is believed to bind to the substrate through hydrogen bonding interactions. Removal of the acidic sulfonamide proton by the tertiary amine group in **1**, followed by a conjugate addition to the alkylidene from its *Si* face, gives rise to the major stereoisomer.

In conclusion, we have developed a new approach for the asymmetric preparation of biologically important 2-aryl-2,3-

(11) (a) Zhu, Q.; Lu, Y. *Org. Lett.* **2008**, *10*, 4803. (b) Najera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547. (c) Kundig, E. P.; Cunningham, A. F., Jr. *Tetrahedron* **1988**, *44*, 6855.

Table 2. Preparation of Various 2-Substituted-2,3-dihydro-4-quinolones[a]



entry	product	t (h)	yield[b] (%)	ee[c] (%)
1	 **6b**	24	98/88	91
2	 **6c**	24	98/87	89
3	 **6d**	28	95/70	98
4[d]	 **6e**	24	96/76	89
5	 **6f**	42	95/90	86
6	 **6g**	24	98/91	93
7	 **6h**	96	93/86	86
8	 **6i**	24	92/88	84
9	 **6j**	48	97/85	78

[a] Reactions were performed with **4** (0.05 mmol), **1** (0.005 mmol) and 4 Å molecular sieves in anhydrous toluene (0.2 mL) at 0 °C for the first step; 0.05 mmol TsOH in toluene (0.2 mL) was used for the second step. [b] Isolated yields for both steps. [c] ee value was determined by HPLC analysis on a chiral stationary phase. [d] The first step was performed at −30 °C.

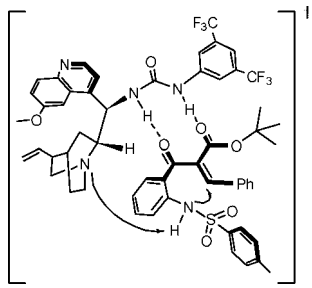


Figure 3. Proposed transition state model.

dihydro-quinolin-4(1*H*)-ones. By installing a sulfonyl group on the nitrogen of anilines and an ester function on the unsaturated ketones, the intramolecular cyclization reactions proceeded in a highly enantioselective manner in the presence of tertiary amine-thiourea organic catalysts, and the subsequent removal of the ester group was realized via an acidic decarboxylative process without affecting the newly generated 2-stereogenic center of the quinolones. The reported procedure represents a practical asymmetric route to 2-substituted-2,3-dihydro-4-quinolones, and this method may find wide applications in the synthesis of other bioactive nitrogen-containing cyclic structures.

Acknowledgment. We thank the National University of Singapore and the Ministry of Education (MOE) of Singapore (R-143-000-362-112) for generous financial support.

Supporting Information Available: Representative experimental procedures for the intramolecular cyclization, the decarboxylative cleavage, and the desulfonylation reaction, HPLC chromatogram, analytical data, and NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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