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Organocatalytic asymmetric conjugate addition of *t*-butyl nitroacetate to *o*-quinone methides: synthesis of optically active α-nitro-β,β-diaryl-propionates†

Ri-long Liu,‡ Xiang-zheng Tang,‡ Xue-jing Zhang, Ming Yan* and Albert S. C. Chan

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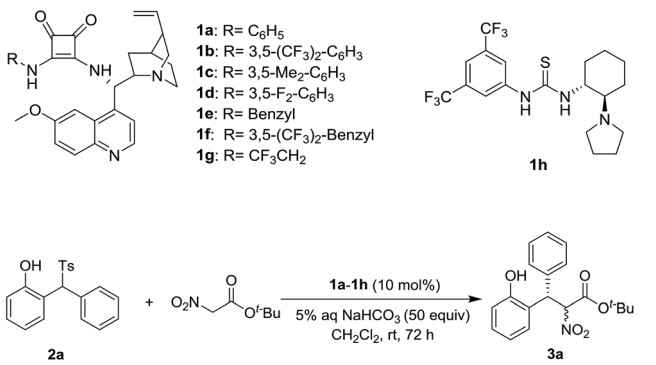
An asymmetric conjugate addition of *t*-butyl nitroacetate to *in situ* generated *o*-quinone methides had been developed. A chiral squamide derived from 9-amino-9-deoxyepiquinine was found to be the efficient catalyst. α-Nitro-β,β-diaryl-propionates could be obtained in good yields and with excellent enantioselectivities.

o-Quinone methides (*o*-QMs) are valuable intermediates for organic synthesis. Although most *o*-QMs are unstable and inseparable, applications of *o*-QMs in organic synthesis have been developed.[1] In recent years, great progress has been made in asymmetric reactions with *o*-QMs.[2] A number of organocatalytic transformations with *o*-QMs have also been explored. Han and co-workers reported the quinine-catalyzed asymmetric cycloannulation of *o*-QMs with malononitrile.[3] Zhou and co-workers reported asymmetric addition of thiols and malononitrile to *o*-QMs with bifunctional organocatalysis.[4] Fochi, Bernardi and co-workers developed chiral squamide-catalyzed asymmetric addition of Meldrum's acid, malononitrile and 1,3-dicarbonyl compounds to *o*-QMs.[5] Sun, Rueping, Schneider, Shi, List and co-workers reported a series of asymmetric reactions of *o*-QMs with chiral Brønsted acid catalysts.[6] Ye and co-workers developed asymmetric reactions of *o*-QMs catalyzed by chiral nitrogen heterocyclic carbenes.[7] Very recently, Scheidt and co-workers reviewed the related progresses of organocatalytic reactions of *in situ* generated *o*-QMs.[8]

In recent years, we have developed organocatalytic asymmetric conjugate addition of nitroacetates to β,γ-unsaturated-α-ketoesters.[9] To expand the application of nitroacetates in organocatalytic transformations, we are interesting in the asymmetric conjugate addition of nitroacetates to *o*-QMs.[10,11] The reaction can provide optically active α-nitro-β,β-diaryl-propionates, which are useful intermediates for the synthesis of chiral drugs and natural products. In this paper, we report an organocatalytic conjugate addition of *t*-butyl nitroacetate to *in situ* generated *o*-QMs. A series of α-nitro-β,β-diaryl-propionates could be obtained in good yields and with excellent enantioselectivities.

Based on our previous experiences,[9] a variety of chiral squamides **1a–1g** and thiourea **1h** were chosen as the catalysts (Table 1). The reaction of 2-tosylmethylphenol **2a** and *t*-butyl

Table 1 Screening of organocatalysts[a]



Entry	Catalyst	Yield[b] (%)	Dr[c]	ee[d] (%)
1	**1a**	83	1/1	95/95
2	**1b**	76	1/1	96/96
3	**1c**	68	1/1	95/95
4	**1d**	69	1/1	95/96
5	**1e**	61	1/1	85/84
6	**1f**	76	1/1	86/86
7	**1g**	61	1/1	88/89
8	**1h**	66	1/1	−94/−94

[a] The reactions were carried out with **2a** (0.20 mmol), *t*-butyl nitroacetate (0.4 mmol), **1a–1h** (0.02 mmol) in CH_2Cl_2 (2.5 mL) and 5% aqueous $NaHCO_3$ (16.8 mL) at room temperature for 72 h. [b] Isolated yields of **3a**. [c] The diastereoisomeric ratios were determined by ^1H NMR. [d] The ee values of **3a** were determined by HPLC with a Chiralpak AD-H column.

Institute of Drug Synthesis and Pharmaceutical Process, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China. E-mail: yanming@mail.sysu.edu.cn

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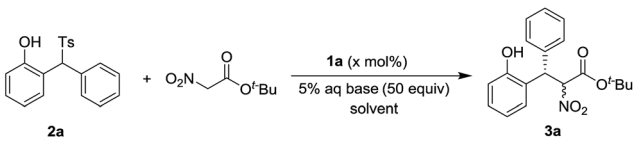
‡ These two authors contribute equally to this study.

nitroacetate was examined and the results are summarized in Table 1. The *in situ* generation of *o*-QM from **2a** in the presence of aqueous sodium bicarbonate was reported by Fochi, Bernardi and co-workers.[5] To our delight, the expected product **3a** was obtained with good yield and enantioselectivity. Almost no diastereoselectivity was achieved in this transformation. The product **3a** was obtained as the equivalent mixture of two diastereoisomers. Among the tested squamide catalysts derived from 9-amino-9-deoxyepiquinine, **1a** afforded the best yield. The 3,5-bistrifluoromethyl, 3,5-bismethyl and 3,5-difluoro substituted analogs **1b–1d** gave lower yields and similar enantioselectivities. Benzyl, 3,5-bistrifluoromethyl benzyl and trifluoroethyl substituted squamides **1e–1g** afforded lower enantioselectivities. The thiourea **1h** provided the enantiomer of **3a** in a moderate yield and with good enantioselectivity.

Using **1a** as the catalyst, the effect of the reaction solvent, the base, the catalyst loading and the reaction temperature was examined and the results are summarized in Table 2. Better enantioselectivity and similar yield were achieved in $CHCl_3$. Lower enantioselectivities were observed in other solvents (Table 2, entries 3–7). The replacement of sodium bicarbonate with potassium bicarbonate led to slightly lower yield (Table 2, entry 8). The use of more basic sodium carbonate, potassium carbonate, and cesium carbonate gave poor yields and enantioselectivities (Table 2, entries 9–11). While less basic sodium acetate and potassium fluoride were examined, low yields and good enantioselectivities were observed (Table 2, entries 12 and 13). The decrease of the catalyst loading gave slightly lower yields and enantioselectivities (Table 2, entries 14 and 15). The reaction at 0 °C gave a poor yield and inferior enantioselectivity (Table 2, entry 16). The higher reaction temperature was found to be detrimental for the enantioselectivity (Table 2, entry 17).

Table 2 Optimization of the reaction conditions[a]

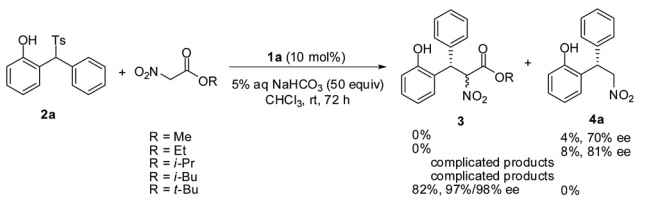


Entry	Solvent	*x*	Base	*T* (°C)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	10	$NaHCO_3$	rt	83	95/95
2	$CHCl_3$	10	$NaHCO_3$	rt	82	97/98
3	$Cl(CH_2)_2Cl$	10	$NaHCO_3$	rt	64	92/92
4	Toluene	10	$NaHCO_3$	rt	51	29/35
5	EtOAc	10	$NaHCO_3$	rt	20	5/5
6	MeO^{t}Bu	10	$NaHCO_3$	rt	36	2/2
7	EtOH	10	$NaHCO_3$	rt	80	4/4
8	$CHCl_3$	10	$KHCO_3$	rt	80	97/97
9	$CHCl_3$	10	Na_2CO_3	rt	23	19/16
10	$CHCl_3$	10	K_2CO_3	rt	25	1/1
11	$CHCl_3$	10	Cs_2CO_3	rt	32	0/0
12	$CHCl_3$	10	NaOAc	rt	24	98/98
13	$CHCl_3$	10	KF	rt	28	89/90
14[d]	$CHCl_3$	5	$NaHCO_3$	rt	80	96/96
15[d]	$CHCl_3$	2	$NaHCO_3$	rt	74	94/94
16	$CHCl_3$	10	$NaHCO_3$	0	20	87/88
17[e]	$CHCl_3$	10	$NaHCO_3$	40	72	95/94

[a] The reactions were carried out with **2a** (0.20 mmol), *t*-butyl nitroacetate (0.4 mmol), **1a** (0.02 mmol) in solvent (2.5 mL) and 5% aqueous base (50 equiv.) at room temperature for 72 h. [b] Isolated yields of **3a**. The diastereoisomeric ratios were found to be 1/1 in all cases by ^{1}H NMR. [c] The ee values of **3a** were determined by HPLC with a Chiralpak AD-H column. [d] The reaction was run for 84 h. [e] The reaction was run for 48 h.

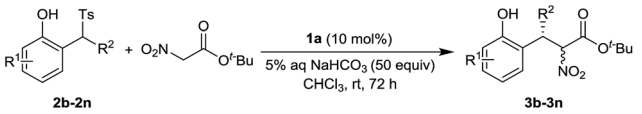
The influence of different ester group of nitroacetates was also investigated and the results are summarized in Scheme 1. The reaction of methyl nitroacetate and ethyl nitroacetate did not give the expected products, instead the decarboxylated product **4a** was obtained in poor yields and with moderate enantioselectivities. Complicated products were observed in the reaction of i-propyl nitroacetate and i-butyl nitroacetate. The LC-MS analysis showed the existence of a small amount of the expected conjugate addition products, but no pure samples could be isolated and characterized. The hydrolysis of these nitroacetates in aqueous sodium bicarbonate possibly accounted for the results.[12] The resistance of *t*-butyl nitroacetate to the basic hydrolysis ensures the good yield.

A variety of 2-tosylmethylphenols **2b–2n** were examined in the reaction and the results are summarized in Table 3. The introduction of 4-methyl, 4-*t*-butyl and 4-methoxyl to the phenyl ring did not affect the yields and enantioselectivities (Table 3, entries 1–3). The substitutions with 5-methoxyl, 6-methoxyl and 4,5-methylenedioxy led to the better yields and excellent enantioselectivities (Table 3, entries 4–6). The 6-methyl substituted substrate **3h** gave the inferior yield, but still with excellent enantioselectivity (Table 3, entry 7). The 6-fluoro substitution was tolerated well. The good yield and excellent enantioselectivity were achieved (Table 3, entry 8). Interestingly, the improved diastereoselectivity was observed in this case. Keeping 5-methoxyl substitution at the left phenyl ring, a number of substrates with different substituents at the right phenyl ring of **2a** were examined. The substitutions with 2-methyl, 2-methoxyl, 4-methyl and 4-methoxyl provided the products with excellent yields and enantioselectivities (Table 3, entries 9–12). While R^2 was changed to a methyl group, excellent yield and moderate enantioselectivity were achieved (Table 3, entry 13). It should be noted that the introduction of 5-methoxyl substitution at the left phenyl ring significantly increases the reactivity of the substrates. Shorten reaction time was required in these cases. 1-(Phenyl(tosyl)methyl)naphthalen-2-ol was prepared and examined under the standard conditions, but no



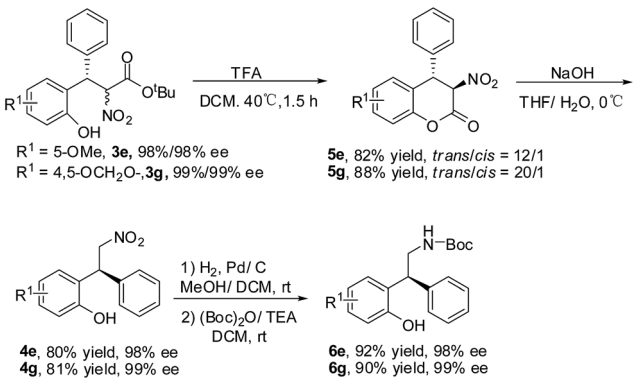
Scheme 1 Effect of ester group in nitroacetates. [a] The reactions were carried out with **2a** (0.20 mmol), nitroacetate (0.4 mmol), **1a** (0.02 mmol) in $CHCl_3$ (2.5 mL) and 5% aqueous $NaHCO_3$ (16.8 mL) at room temperature for 72 h. [b] Isolated yields. [c] The ee values of **4a** were determined by chiral HPLC with a Chiralpak OJ-H column.

Table 3 Examination of the substrate scope[a]

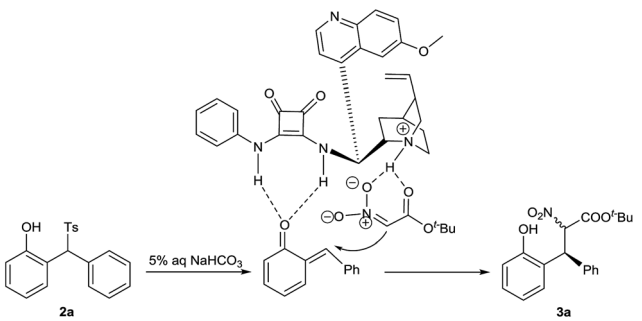


Entry	R^1	R^2	Yield[b] (%)	Dr[c]	ee[d] (%)
1	4-Me	C_6H_5	**3b**, 73	1 : 1	97/98
2	4-^{t}Bu	C_6H_5	**3c**, 80	1 : 1	96/92
3	4-MeO	C_6H_5	**3d**, 80	1 : 1	97/97
4[e]	5-MeO	C_6H_5	**3e**, 98	1 : 1	98/98
5	6-MeO	C_6H_5	**3f**, 95	1 : 1	96/98
6	4,5-OCH_2O–	C_6H_5	**3g**, 92	1 : 1	99/99
7	6-Me	C_6H_5	**3h**, 52	1 : 1	97/95
8	6-F	C_6H_5	**3i**, 81	5 : 1	97/97
9[e]	5-MeO	2-Me–C_6H_4	**3j**, 98	1 : 1	99/99
10[e]	5-MeO	2-MeO–C_6H_4	**3k**, 90	1 : 1	97/97
11[e]	5-MeO	4-Me–C_6H_4	**3l**, 98	1 : 1	96/98
12[e]	5-MeO	4-MeO–C_6H_4	**3m**, 99	1 : 1	99/98
13[f]	5-MeO	Me	**3n**, 94	1.5 : 1	83/86

[a] The reactions were carried out with **2b–2n** (0.20 mmol), *t*-butyl nitroacetate (0.4 mmol), catalyst **1a** (0.02 mmol) in $CHCl_3$ (2.5 mL) and 5% aqueous $NaHCO_3$ (16.8 mL) at room temperature for 72 h. [b] Isolated yields. [c] The diastereoisomeric ratios were determined by ^{1}H NMR. [d] The ee values were determined by HPLC with a Chiralpak AD-H column. [e] The reaction was run for 24 h. [f] The reaction was run for 40 h.



Scheme 2 Transformation of the product **3e** and **3g**.



Scheme 3 Proposed reaction mechanism.

expected product was obtained. The big steric hindrance of this substrate possibly prohibited the reaction.

The transformation of the product **3e** and **3g** was explored (Scheme 2).[13] The ester exchange was achieved by the treatment of **3e**/**3g** with TFA. The lactones **5e**/**5g** were obtained with good yields and diastereoselectivities.[14] The basic hydrolysis of **5e**/**5g** gave the decarboxylation products **4e**/**4g**. The absolute configuration of **4g** was determined as *S* by the comparison of the optical rotation with the reported data.[15] The reduction of **4e**/**4g** and the protection of the amino group with $(Boc)_2O$ provided **6e**/**6g** in good yields and without the erosion of optical purity.

A tentative reaction mechanism is suggested in Scheme 3. *o*-QM is generated from 2-tosylmethylphenol **2a** in the presence of aqueous sodium bicarbonate. The double hydrogen bonding of *o*-QM with catalyst **1a** increases its electrophilic reactivity. In the meantime, **1a** abstracts a proton from *t*-butyl nitroacetate to give the nitro enolate, which is drawn close to *o*-QM by the hydrogen bonding with the ammonium cation. The subsequent attack from *si*-face of *o*-QM provides the product **3a**.

Conclusions

In conclusion, we have developed an organocatalytic asymmetric reaction of *o*-QMs with *t*-butyl nitroacetate. 2-Tosylmethylphenols could be used as the suitable precursors of *o*-QMs in the presence of aqueous sodium bicarbonate. A chiral squamide derived from 9-amino-9-deoxyepiquinine was identified as the superior catalyst. A variety of *t*-butyl α-nitro-β,β-diaryl-propionates were prepared in good yields and with excellent enantioselectivities. The further elaboration of the products provided the useful chiral intermediates for the synthesis of drugs and natural products.

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12 The reaction of **2a** with nitromethane under the standard conditions is not successful. No product **4a** was observed in the reaction mixture. The lower reactivity of nitromethane comparing with nitroacetates possibly accounts for the result.

13 The direct reduction of nitro group of **3e** and **3g** was not successful *via* general reduction methods (such as the catalytic hydrogenation over Pd/C, Pt/C, RANEY®-Ni, and the reduction with Zn, Sn, Fe powder). The big steric hindrance of **3e** and **3g** may prohibit the reaction of the nitro group.

14 The reduction of **5e**/**5g** was not successful despite extensive efforts were made (the catalytic hydrogenation over Pd/C, Pt/C, RANEY®-Ni, and the reduction with Zn, Sn, Fe powder). We think the big steric hindrance of **5e** and **5g** hampers the reduction.

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