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Synthesis of Sulfur-Substituted α-Stereogenic Amides and Ketones: Highly Enantioselective Sulfa-Michael Additions of 1,4-Dicarbonylbut-2-enes

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Abstract: Conjugate addition to 1,4-dicarbonylbut-2-enes will generate an α-stereogenic center with respect to one of the carbonyl groups, which informally, can be considered as an inversion of normal reactivity patterns or *umpolung* protocol. In this paper, the addition of *tert*-butyl mercaptan to 1,4-dicarbonylbut-2-enes including (*E*)-4-oxo-4-arylbutenamides and (*E*)-4-oxo-4-arylbutenones has been developed, to synthesize a series of chiral sulfur-substituted α-stereogenic amides and ketones in high regioselectivity and enantioselectivity (up to 98% *ee*).

Keywords: asymmetric catalysis; 1,4-dicarbonylbut-2-enes; organocatalysis; α-stereogenic amides and ketones; sulfa-Michael addition

Molecules with sulfur-containing frameworks are common key building blocks in pharmaceutical and natural products.[1] Many chiral sulfur-containing compounds have become useful ligands,[2] organocatalysts,[3] and chiral reagents or auxiliaries.[4] The asymmetric Michael addition of thiols to activated alkenes enables an efficient construction of valuable optically active sulfur-containing compounds.[5] Both asymmetric organometallic and organocatalytic approaches for sulfa-Michael additions have been extensively studied by several research groups.[6] However, most of them resulted in the formation of sulfides bearing a stereogenic center β to an electron-withdrawing group since the β-carbon often behaves as an electrophile center.

Enantioselective protonation of an enolate, generated from the conjugate addition of thiols to activated terminal alkenes, has been demonstrated to be highly desirable to construct α-stereogenic sulfides,[6n,p,r] however, the sulfur atom is not embedded to the stereogenic center. Recently, Xiao et al have developed an asymmetric sulfa-Michael addition of aromatic thiols to β,β-disubstituted nitroalkenes to access chiral $\beta^{2,2}$-amino acids, which produced the sulfur-substituted α-stereogenic esters.[6m] By introducing an electron-withdrawing nitro group at the β-position of acrylate, the reactivity of its α-carbon is inversed from a nucleophile to an electrophile. Therefore, this could informally be considered as an inversion of normal reactivity patterns or *umpolung* reactivity.[7]

Since both amides and ketones with α-stereogenic centers are useful building blocks for the synthesis of biologically active compounds,[8] the asymmetric synthesis of them has been attractive to chemists.[9] We have developed a highly enantio- and regioselective protocol to construct carbon-substituted α-stereogenic amides and ketones[9a] during our investigations of chiral bicyclic guanidine-catalyzed reactions.[6n,p,9a,10] The acceptors were designated as 1,4-dicarbonylbut-2-enes including (*E*)-4-oxo-4-arylbutenamides and (*E*)-4-oxo-4-arylbutenones; using a similar *umpolung* concept to generate α-stereogenic amides and ketones. It is noteworthy that sulfur-substituted α-stereogenic ke-

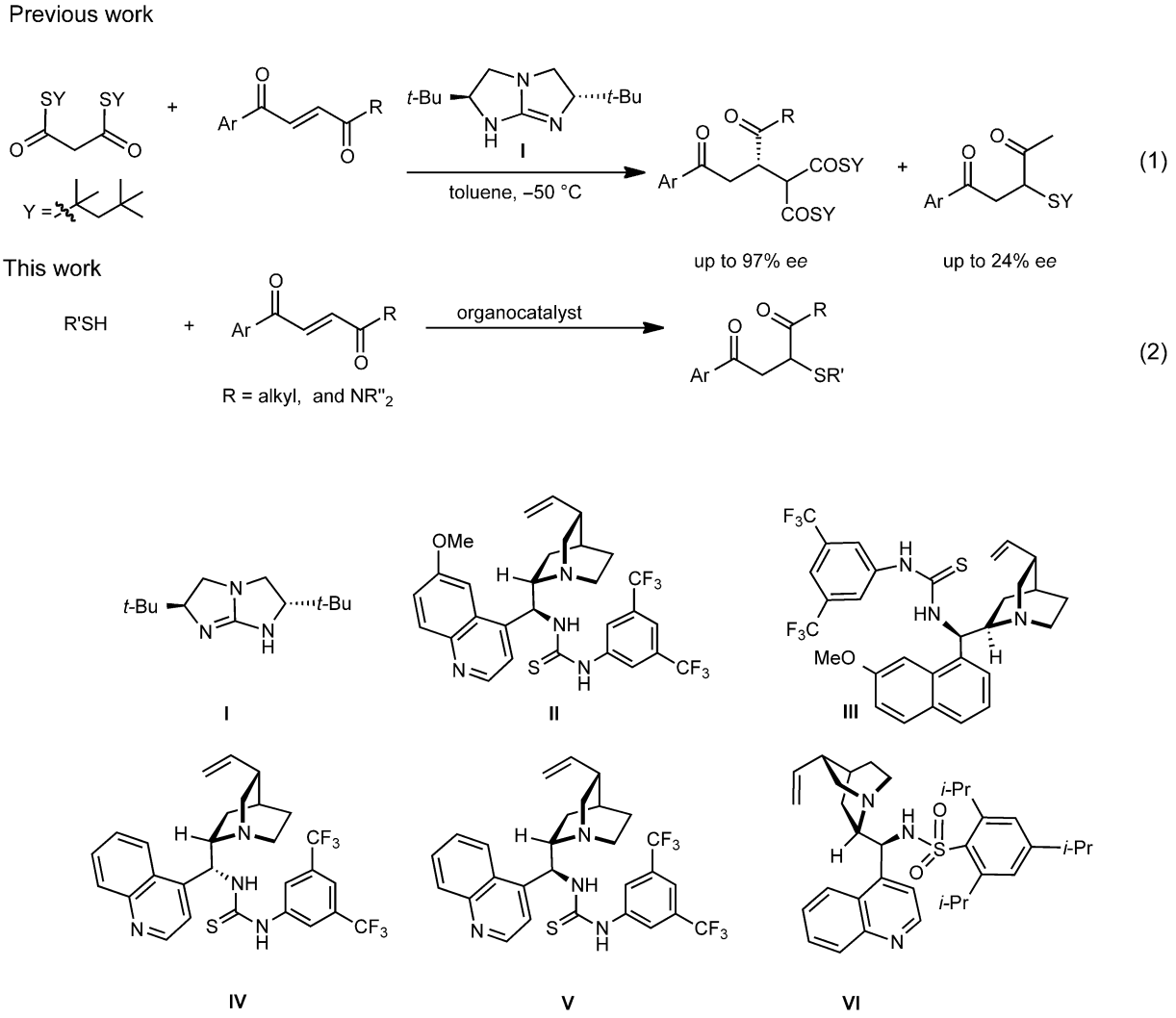
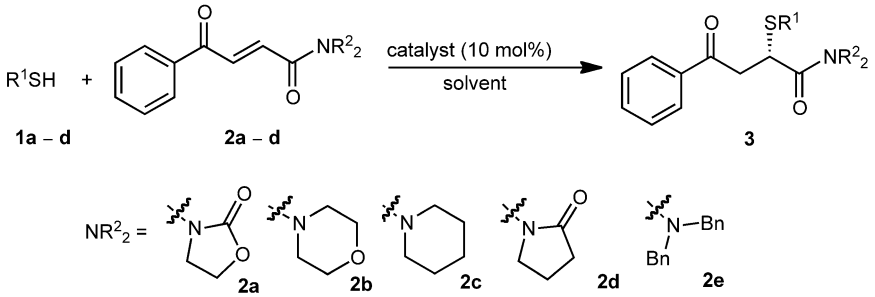


Figure 1. Structures of various bifunctional organocatalysts **I–VI**.

tones as side products were detected in high regioselectivities but poor enantioselectivities [Eq. (1)]. Thus, we are keen to develop a highly enantio- and regioselective synthesis of sulfur-substituted α-stereogenic amides and ketones *via* the sulfa-Michael addition between thiols and 1,4-dicarbonylbut-2-enes [Eq. (2)].

In our exploratory studies, *tert*-butyl mercaptan (TBM) **1a** was subjected to Michael conjugation with (*E*)-4-oxo-4-arylbutenamide **2a** catalyzed using 10 mol% guanidine **I** (Figure 1) in toluene at 0 °C (Table 1, entry 1). We found that the reaction proceeded efficiently to afford the adduct **3aa** in excellent yield but moderate enantioselectivity (56% *ee*). Further investigation did not improve the enantioselectivity. Therefore, we tested other bifunctional catalysts **II–VI** (Figure 1) derived from *Cinchona* alkaloids (Table 1, entries 2–6).[11] The highest enantioselectivity (78% *ee*) of **3aa** was achieved in the presence of 10 mol% **IV** as catalyst (Table 1, entry 4). Unsatisfactory results were obtained under the same conditions when other thiols **1b–d** were used as donors and (*E*)-4-oxo-4-arylbutenamides with different amide moieties **2b–e** were employed as acceptors (Table 1, entries 7–13). In combination with **IV** as the optimized organocatalyst, **1a** and **2a** were chosen as model substrates for further optimization. Lowering the temperature to −20 °C effected an improvement of the enantioselectivity (Table 1, entry 14). A screen of different solvents revealed that dichloromethane was the best reaction medium (Table 1, entries 15–17). Finally, **3aa** could be obtained in high yield and in 92% *ee* in dichloromethane at −50 °C (Table 1, entries 18 and 19). The reaction rate was increased about twice without compromising the enantio- and regioselectivity by increasing the amount of **1a** from 3.0 to 5.0 equivalents. With the optimized reaction conditions, **1c** and **1d** as donors were tested with acceptor **2a**. However, the enantioselectivities were not improved (Table 1, entries 20 and 21). The reaction

Table 1. Asymmetric addition of thiols **1a–d** to (*E*)-4-oxo-4-arylbutenamides **2a–d** catalyzed by different bifunctional organocatalysts **I–VI**.[a]



Entry	1	2	Catalyst	Solvent	*T* [°C]	*t* [h]	3	Yield [%][b]	*ee* [%][c]
1	**1a** [*tert*-butyl]	**2a**	**I**	toluene	0	0.5	**3aa**	99	56[d]
2	**1a** [*tert*-butyl]	**2a**	**II**	toluene	0	48	**3aa**	78	-33
3	**1a** [*tert*-butyl]	**2a**	**III**	toluene	0	48	**3aa**	64	72
4	**1a** [*tert*-butyl]	**2a**	**IV**	toluene	0	48	**3aa**	63	78
5	**1a** [*tert*-butyl]	**2a**	**V**	toluene	0	48	**3aa**	80	-32
6	**1a** [*tert*-butyl]	**2a**	**VI**	toluene	0	48	**3aa**	Trace	-15
7	**1b** [*n*-propyl]	**2a**	**IV**	toluene	0	9	**3ba**	90	60
8	**1c** [isopropyl]	**2a**	**IV**	toluene	0	9	**3ca**	79	18
9	**1d** [Bn]	**2a**	**IV**	toluene	0	22	**3da**	70	44
10	**1a** [*tert*-butyl]	**2b**	**IV**	toluene	0	24	**3ab**	48	48
11	**1a** [*tert*-butyl]	**2c**	**IV**	toluene	0	24	**3ac**	54	64
12	**1a** [*tert*-butyl]	**2d**	**IV**	toluene	0	24	**3ad**	48	77
13	**1a** [*tert*-butyl]	**2e**	**IV**	toluene	0	96	**3ae**	56	16
14[e]	**1a** [*tert*-butyl]	**2a**	**IV**	toluene	−20	72	**3aa**	78	84
15[e]	**1a** [*tert*-butyl]	**2a**	**IV**	CH_2Cl_2	−20	24	**3aa**	89	88
16[e]	**1a** [*tert*-butyl]	**2a**	**IV**	$CHCl_3$	−20	48	**3aa**	58	86
17[e]	**1a** [*tert*-butyl]	**2a**	**IV**	DCE	−20	64	**3aa**	80	88
18[e]	**1a** [*tert*-butyl]	**2a**	**IV**	CH_2Cl_2	−50	96	**3aa**	57	92
19[f]	**1a** [*tert*-butyl]	**2a**	**IV**	CH_2Cl_2	−50	48	**3aa**	90	92 [g]
20[f]	**1c** [isopropyl]	**2a**	**IV**	CH_2Cl_2	−50	36	**3ca**	95	24
21[f]	**1d** [Bn]	**2a**	**IV**	CH_2Cl_2	−50	24	**3da**	90	45
22[f]	**1e** [Ph]	**2a**	**IV**	CH_2Cl_2	−50	12	**3ea**	87	55

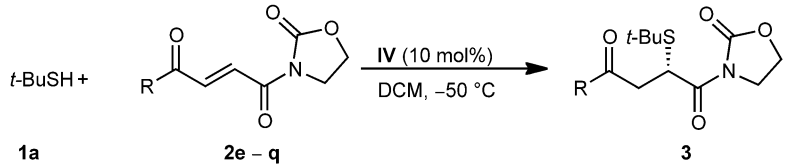
[a] Unless otherwise noted, reactions were performed with 0.03 mmol of **1a–d**, 0.02 mmol of **2a–d**, and 0.002 mmol of catalyst in 0.2 mL solvent.
[b] Isolated yield.
[c] Chiral HPLC.
[d] At −50 °C, reaction was finished in 2 h but the *ee* was the same.
[e] 0.06 mmol of **1a**, 0.02 mmol of **2a**, and 0.002 mmol of **IV** in 0.2 mL solvent.
[f] 0.25 mmol of **1a**, 0.05 mmol of **2a**, and 0.005 mmol of **IV** in 0.5 mL solvent.
[g] 0.5 mmol scale, $t = 43$ h, yield = 99% (166.7 mg), *ee* = 92%.

between the aromatic thiol **1e** and **2a** was fast but gave only moderate enantioselectivity (Table 1, entry 22).

Various (*E*)-4-oxo-4-arylbutenamides **2e**–**p** containing 2-oxazolidinone as amide moiety were examined, and the results are summarized in Table 2. Excellent *ee* values (up to 97% *ee*) were obtained under the established reaction conditions. The results revealed that the enantioselectivity of the reaction was not sensitive to the electronic effects of substituted groups on the aromatic rings. Reaction rates were determinately affected by tuning the electronic effects of the substrates. Thus, substrates **2i**, **2j–l**, **2n** and **2o** and the electron-rich heteroaromatic **2p** required 10 equivalents of **1a** for completion in reasonable reaction times (Table 2, entries 5–8 and 10–12). The reigochemistry of the adducts was confirmed by NOE analysis of **3ao**.[12] (*E*)-4-Oxo-4-methylbutenamide **2q**, containing an aliphatic ketone moiety, was tested in the reaction with **1a** (Table 2, entry 13). We found that the reaction was very slow even at higher temperature (−20 °C) with moderate enantioselectivity.

Other than (*E*)-4-oxo-4-arylbutenamides, (*E*)-4-oxo-4-arylbutenones **4** were also used as acceptors in

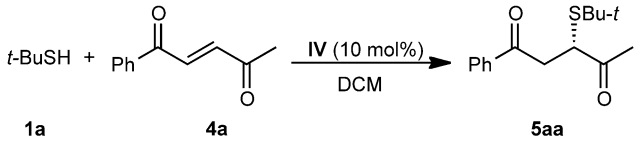
Table 2. Asymmetric addition of TBM **1a** to (*E*)-4-oxo-4-arylbutenamides **2e–q** catalyzed by **IV**.[a]



Entry	**2 [R]**	*t* [h]	**3**	Yield [%][b]	*ee* [%][c]
1	**2e** [*p*-CF_3-C_6H_4]	60	**3ae**	80	94
2	**2f** [*p*-F-C_6H_4]	56	**3af**	84	92
3	**2g** [*p*-Cl-C_6H_4]	42	**3ag**	97	94
4	**2h** [*p*-Br-C_6H_4]	29	**3ah**	90	97
5[d]	**2i** [*p*-Ph-C_6H_4]	60	**3ai**	84	95
6[d]	**2j** [*m*-CN-C_6H_4]	60	**3aj**	80	90
7[d]	**2k** [*m*-Br-C_6H_4]	60	**3ak**	92	94
8[d]	**2l** [*m*-MeO-C_6H_4]	48	**3al**	80	92[e]
9	**2m** [*o*-NO_2-C_6H_4]	29	**3am**	75	86
10[d]	**2n** [*o*-F-C_6H_4]	60	**3an**	85	91[e]
11[d]	**2o** [2-naphthyl]	50	**3ao**	91	98
12[d]	**2p** [2-thienyl]	90	**3ap**	81	92
13[e]	**2q** [Me]	72	**3aq**	45	62

[a] Unless otherwise noted, reactions were performed with 0.25 mmol of **1a**, 0.05 mmol of **2**, and 0.005 mmol of catalyst in 0.5 mL solvent.
[b] Isolated yield.
[c] Chiral HPLC.
[d] Reactions were performed with 0.50 mmol of **1a**, 0.05 mmol of **2**, and 0.005 mmol of catalyst in 0.5 mL solvent.
[e] The reaction was conducted at −20 °C.

Table 3. Investigation of conditions for the asymmetric addition of TBM **1a** to (*E*)-4-oxo-4-arylbutenones **4a** catalyzed by **IV**.[a]



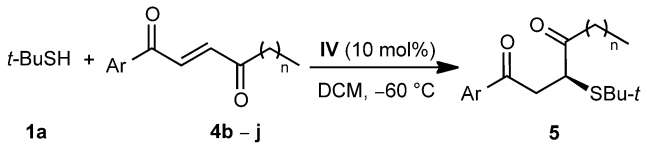
Entry	**1a**:**4a**	**1a**:DCM	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	5:1	–	−50	96	98	80
2	10:1	–	−50	42	56	80
3	20:1	–	−50	42	90	81
4[d]	–	1:3	−50	29	80	80
5[d]	–	1:1	−50	9	99	82
6[d]	–	1:1	−60	17	99	86
7[e]	–	2:1	−60	9	93	86[f]

[a] Unless otherwise noted, reactions were performed with 0.02 mmol scale in 0.2 mL dichloromethane.
[b] Isolated yield.
[c] Chiral HPLC.
[d] Reactions were performed with 0.02 mmol scale in 0.2 mL mixed solvent of BSM **1a** and dichloromethane with different ratios.
[e] Reactions were performed with 0.05 mmol scale in 0.5 mL solvent (**1a**:DCM = 2:1).
[f] 0.5 mmol scale, *t* = 12 h, yield = 80% (106.4 mg), *ee* = 86%.

the asymmetric sulfa-Michael additions. The reaction between **1a** and **4a** with a 5:1 ratio was catalyzed by 10 mol% **IV** in dichloromethane at −50 °C (Table 3, entry 1). After 96 h, the adduct **5aa** was obtained with 98% yield and 80% *ee*. The reaction rate can be improved by increasing the amount of **1a** (Table 3, entries 2 and 3). It is well known that highly concentrated reaction conditions can enhance the reaction rate in organic synthesis. Thus, **1a** which has a high melting point (−1.1 °C) was tested as co-solvent with DCM to improve the reaction rate (Table 3, entries 4–7). We found that the reaction rate was accelerated at higher concentrations without compromising the enantioselectivity when the ratio of **1a**:DCM was increased from 1:3 to 1:1. The best ratio was found to be 2:1, and 86% *ee* of **5aa** in excellent yield was achieved after 9 h at −60 °C (Table 3, entry 7). Under the high concentration conditions, less than 5% of the regioisomer of **5aa** was detected from crude ^{1}H NMR. However, the surplus of **1a** and the regioisomer of **5aa** could be easily removed by flash column chromatography.

Using the optimized conditions, (*E*)-4-oxo-4-arylbutenones **4b–j** (Table 4) were subjected to sulfa-Michael addition with TBM **1a**. Most of reactions were completed within 20 h. The adducts **5ab–aj** were obtained in high yields and good to excellent *ee*s. The regioisomers for some reactions were detected in

Table 4. Asymmetric addition of TBM **1a** to (*E*)-4-oxo-4-arylbutenones **4b–j** catalyzed by **IV**.[a]



1a **4b – j** **5**

Entry	4 [Ar]	*n*	*t* [h]	5	Yield [%][b]	*ee* [%][c]
1	**4b** [*p*-CF_3-C_6H_4]	0	15	**5ab**	78	87
2	**4c** [*p*-F-C_6H_4]	0	6	**5ac**	87	90
3	**4d** [*p*-Cl-C_6H_4]	0	6	**5ad**	91	86
4	**4e** [*p*-Br-C_6H_4]	0	6	**5ae**	80	86
5	**4f** [*p*-MeO-C_6H_4]	0	33	**5af**	86	90
6	**4g** [*m*-NO_2-C_6H_4]	0	20	**5ag**	87	90
7	**4h** [*m*-MeO-C_6H_4]	0	6	**5ah**	90	90
8	**4i** [2-thienyl]	0	30	**5ai**	91	88
9	**4j** [*m*-MeO-C_6H_4]	2	15	**5aj**	75	87

[a] Unless otherwise noted, reactions were performed with 0.05 mmol scale in 0.5 mL solvent (**1a**:DCM = 2:1).
[b] Isolated yield.
[c] Chiral HPLC.

small amount (less than 10%). The absolute configurations of the sulfa-Michael addition products were assigned as *S* based on an *X*-ray crystallographic analysis of single crystal **5ad**.[13] Furthermore, we demonstrated that the α-stereogenic ester **6** could be smoothly achieved from the corresponding α-stereogenic amide **3ag** without compromising the *ee* value [Eq. (3)].[7j]

In summary, we have developed a highly enantioselective and regioselective organocatalytic sulfa-Michael addition of *tert*-butyl mercaptan to (*E*)-4-oxo-4-arylbutenamides and (*E*)-4-oxo-4-arylbutenones, which provides a new avenue to the construction of the chiral sulfur-containing centers α to the amide and ketone groups. To the best of our knowledge, this is the first example of the organocatalyzed enantioselective synthesis of sulfur-substituted α-stereogenic amides and ketones. Further studies on the synthesis of other useful chiral α-stereogenic amides and ketones using different donors are undergoing in our laboratories.

Experimental Section

General Procedure for the Addition of *tert*-Butyl Mercaptan 1a to (*E*)-4-Oxo-4-arylbutenamides 2a and 2e–p Catalyzed by IV

(*E*)-4-Oxo-4-arylbutenamides **2a**, **2e–p** (0.05 mmol, 1 equiv.) and **IV** (2.8 mg, 0.005 mmol, 0.1 equiv.) were dissolved in dichloromethane (500 μL) in 4-mL sample vials and stirred at the required temperature (−50 to −20 °C) for 30 min. Then *tert*-butyl mercaptan **1a** (0.25 mmol/28 μL or 0.50 mmol/56 μL) was added. The reacting mixtures were stirred and maintained at the desired temperature and the reaction progress was monitored by TLC. Upon complete consumption of the (*E*)-4-oxo-4-arylbutenamides **2a** and **2e–p**, the reaction mixtures were loaded onto a short silica gel column, followed by separation with flash chromatography using gradient elution with PE (petroleum ether)/EA mixtures (10:1 to 2:1). After the removal of solvent under vacuum, products **3aa** and **3ae–ap** were obtained.

General Procedure for the Addition of *tert*-Butyl Mercaptan 1a to (*E*)-4-Oxo-4-arylbutenones 4a–j Catalyzed by IV

Catalyst **IV** (2.8 mg, 0.005 mmol, 0.1 equiv.) and *tert*-butyl mercaptan **1a** (333 μL) were dissolved in dichloromethane (167 μL) in 4-mL sample vials. After stirring at −60 °C for 30 min, (*E*)-4-oxo-4-arylbutenones **4a–j** (0.05 mmol, 1 equiv.) was added. The reaction mixtures were stirred at −60 °C and monitored by TLC. Upon complete consumption of the (*E*)-4-oxo-4-arylbutenones **4a–j**, the reaction mixtures were loaded onto a short silica gel column, followed by flash chromatography using gradient elution with PE (petroleum ether)/EA mixtures (20:1 to 10:1). Removing the solvent under vacuum, afforded products **5aa** and **5ae–aj**.

Supporting Information

Experimental procedures, characterization and spectroscopic data (PDF) are available in the Supporting Information.

Acknowledgements

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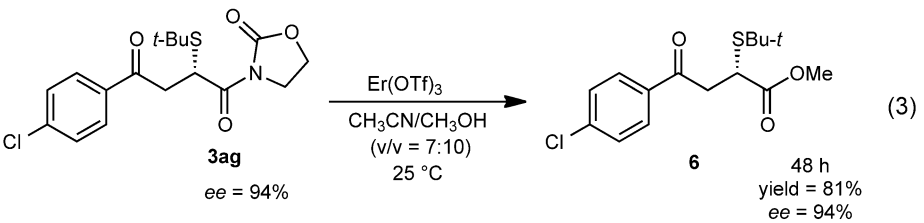

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[12] See the Supporting Information for details.

[13] CCDC 817603 (**5ad**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

