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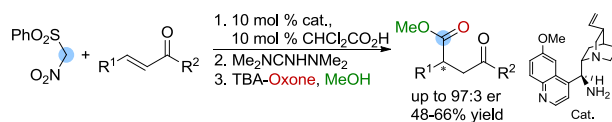
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ABSTRACT

A feasible method has been developed for the enantioselective synthesis of α-stereogenic γ-keto esters. Employing nitro(phenylsulfonyl)methane as an acyl anion equivalent, the integrated Michael addition reaction-oxidative methanolysis protocol allows the preparation of various γ-keto esters with high optical purities.

γ-Keto esters are amongst the most important synthetic feedstocks for constructing complex molecules. Although various methods have been developed for the preparation of racemic γ-keto esters,[1] majority of them use arduous synthetic procedures and/or utilize scarce reagents. Feasible protocols toward these compounds are thus ardently sought. Enantioselective synthesis of α-stereogenic γ-keto esters is mainly achieved through the conjugate addition of various nucleophiles to 4-oxo-4-butenoates (Eq. 1, Scheme 1).[2] Although metal-catalyzed asymmetric cyanation of α,β-unsaturated carbonyl compounds paves an alternative route to γ-keto esters,[3] the method is disadvantageous in that it employs hazardous cyanides that can react via a possible undesirable 1,2-addition pathway (Eq. 2, Scheme 1).[4]

The above mentioned challenges are essentially due to the incompatible donating/accepting natures of the β- and the γ-carbon atoms in γ-keto ester backbones. Therefore implementation of an organocatalyzed conjugate addition merged with an umpolung strategy[5] could provide a robust solution to these issues (Eq. 3, Scheme 1).[6,7] In principle, this proposal could be achieved by integrating

[1] (a) Russell, G. A.; Ochrymowycz, L. A. *J. Org. Chem.* **1969**, *34*, 3624-3626; (b) Miyashita, M.; Yamaguchi, R.; Yoshikoshi, A. *J. Org. Chem.* **1984**, *49*, 2857-2863; (c) Miyashita, M.; Yanami, T.; Kumazawa, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1984**, *106*, 2149-2156; (b) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3493-3494; (c) Kubota, Y.; Nemoto, H.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 7195-7196; (d) Csáký, A. G.; Plumet, J. *Chem. Soc. Rev.* **2001**, *30*, 313-320; (e) Yan, M.; Zhao, W.-J.; Huang, D.; Ji, S.-J. *Tetrahedron Lett.* **2004**, *45*, 6365-6367; (f) Wang, W.; Xu, B.; Hammond, G. B. *J. Org. Chem.* **2009**, *74*, 1640-1643; (g) Barluenga, J.; Lonzi, G.; Riesgo, L.; Tomás, M.; López, L. A. *J. Am. Chem. Soc.* **2011**, *133*, 18138-18141; (h) Gururaja, G. N.; Mobin, S. M.; Namboothiri, I. N. N. *Eur. J. Org. Chem.* **2011**, 2048-2052.

[2] The related Friedel-Crafts reaction, (a) Evans, D. A.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 2249-2252; (b) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029-10041; (c) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403-1405; the related Michael addition, (d) Wang, Z.; Chen, D.; Yang, Z.; Bai, S.; Liu, X.; Lin, L.; Feng, X. *Chem. Eur. J.* **2010**, *16*, 10130-10136; Wang, Z.; Yang, Z.; Chen, D.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2011**, *50*, 4928-4932.

[3] A typical method for methanolysis of cyanide-enone adducts, see: Davey, W.; Tivey, D. J. *Chem. Soc.* **1958**, 1230-1236.

[4] (a) Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 6072-6073; (b) Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 8862-8863; (c) Kurono, N.; Nii, N.; Sakaguchi, Y.; Uemura, M.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 5541-5544.

[5] Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239-258.

[6] The Stetter reaction has been utilized in the asymmetric synthesis of 1,4-dicarbonyl compounds, see: (a) Stetter, H. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 639-647; (b) Christmann, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 2632-2634; (c) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988-3000; (d) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182-1195; (e) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511-3522.

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an enantioselective malononitrile-enone conjugate addition[8] with an oxidative degradation of the adducts (Eq. 4, Scheme 1).[9] Nonetheless, the applicability of this approach is significantly diminished by the acute toxicity of malononitrile (via its metabolism to CN⁻ in the body).[10]

Scheme 1. Enantioselective Synthesis of γ-Keto Esters
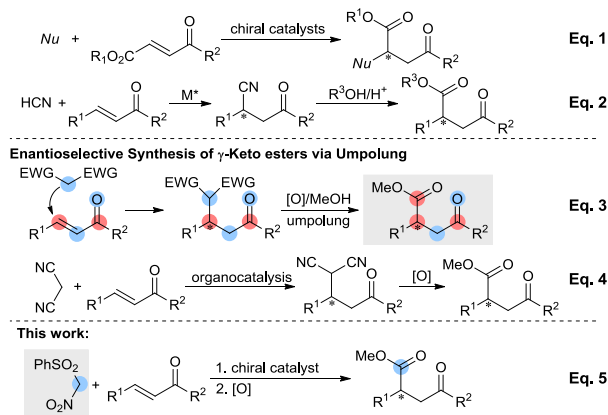
Addressing such an inherent synthetic challenge, we envisaged nitro(phenylsulfonyl)methane (NSM, **1**) to be a versatile acyl anion precursor due to its superior properties over other active methylene pronucleophiles. First, among strong carbon acids, NSM (pK_a ≈ 7 in DMSO)[11] and its α-substituted derivatives can undergo ready deprotonation to form the corresponding anions that can serve as nucleophiles in many transformations.[12] Secondly, the oxidative degradation of primary nitroalkanes (NO_2CH_2R)[13] and primary sulfones (RSO_2CH_2R')[14] usually requires harsh reaction conditions, such as utilization of strong bases and/or oxidants. In comparison, the oxidative methanolysis of nitro(phenylsulfonyl)methyl moiety (NO_2CHSO_2Ph) can be achieved under considerably milder conditions.[15] In

particular, α-fluoro-α-nitro(phenylsulfonyl)methane (FNSM) has been found to participate in various asymmetric conjugate addition reactions, which further validates the analogous NSM as a viable pronucleophile.[16] To the best of our knowledge, NSM is also user-benign, therefore prevailing over other highly toxic acyl anion equivalents, such as malononitrile and HCN. In spite of its vast potential as an acyl precursor, NSM is disadvantaged by its high cost and limited synthetic accessibility.[12b,16e,17] To overcome this obstacle, our initial efforts focused on developing a facile preparative approach toward NSM. By modifying a known procedure,[18] NSM can be obtained on a 40 g-scale without advanced purification techniques (Scheme 2).

Scheme 2. Improved Preparation of NSM.
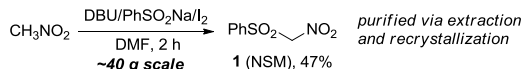
With readily accessible NSM in hand, we performed its thiourea-catalyzed Michael reaction[19] under the conditions employed for that of FNSM (Entries 1-7, Table 1, see SI for details).[16a] However, the reaction with NSM was found to be very sluggish (Entries 1 and 2, Table 1). This is similar to the observation that dinitromethane is less reactive than fluorodinitromethane in the Michael reaction[20] owing to α-fluorine effects.[21]

[8] For selected examples of non-transition metal-catalyzed asymmetric conjugate addition of malononitrile, see: (a) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313-1317; (b) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652-12653; (c) Li, X.; Cun, L.; Lian, C.; Zhong, L.; Chen, Y.; Liao, J.; Zhu, J.; Deng, J. *Org. Biomol. Chem.* **2008**, *6*, 349-353; (d) Naka, H.; Kanase, N.; Ueno, M.; Kondo, Y. *Chem. Eur. J.* **2008**, *14*, 5267-5274; (e) Shi, J.; Wang, M.; He, L.; Zheng, K.; Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2009**, 4711-4713; (f) Pansare, S. V.; Lingampally, R. *Org. Biomol. Chem.* **2009**, *7*, 319-324.
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M.; Madsen, R.; Guile, S. D.; Brown, B. *J. Am. Chem. Soc.* **2000**, *122*, 5947-5956.
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[17] NSM can be obtained via the oxidation of PhSCH$_2$NO$_2$, which can be prepared using PhSCl and NaCH$_2$NO$_2$, see: (a) Barrett, A. G. M.; Dhanak, D.; Graboski, G. G.; Taylor, S. J. *Org. Synth.* **1990**, *68*, 8-13; or using PhSCH$_2$N$_3$ and F$_2$/H$_2$O/CH$_3$CN system, see: (b) Carmeli, M.; Rozen, S. *J. Org. Chem.* **2006**, *71*, 4585–4589.
[18] Based on a known procedure, Weigl, U.; Heimberger, M.; Pierik, A. J.; Rétey, J. *Chem. Eur. J.* **2003**, *9*, 652-660. See SI for details.
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We thus increased the reaction concentration to 2 M, which led to remarkable enhancements in reaction yields (Entries 3-6, Table 1). Oxidative methanolysis of the adduct (**3a**) afforded the desired γ-keto ester (**4a**) with good enantiomeric ratios (*er*), indicating the essential stereochemical stability of the α-carbon in the adduct and the product. Nevertheless, attempts to improve *er* by lowering reaction temperatures resulted in a drastic decrease in yields due to the insufficient solubility of the substrates under the reaction conditions (Entry 7, Table 1). It is also worth noting that the solubilities of many enones can marginally reach the required high concentration (2 M) even at room temperature, therefore diminishing the applicability of the reaction conditions.

Table 1. Thiourea-Catalyzed Synthesis of γ-Keto Esters.

entry	catalyst	temp (°C)	solvent	yield/conv of 3a (%)	er of 4a[e]
1	QN-1	20 °C	CDCl₃	6[a]	-
2	QN-1	20 °C	Toluene	5[a]	-
3	QN-1	20 °C	Toluene[c]	90[b]	93:7
4	C-1	20 °C	Toluene[c]	94[b]	86:14
5	QN-1	20 °C	CH₂Cl₂[c]	87[b]	89:11
6	QN-1	20 °C	Xylenes[c]	95[b]	94:6
7	QN-1	-5 °C	CH₂Cl₂[c,d]	0[a]	-

One-Pot Procedure[f]

entry	catalyst	solvent	yield (%) of 4a[b]	er of 4a[e]
8	CD-2	CH₂Cl₂	46	20:80
9	CN-2	CH₂Cl₂	46	83:17
10	QN-2	CH₂Cl₂	52	18:82
11	QD-2	CH₂Cl₂	40	81:19

[a] Conversions to **3a**, determined by ¹H NMR; [b] isolated yields; [c] performed with **1** at 2 M conc.; [d] performed without stirring; [e] measured by chiral HPLC; [f] the oxidative methanolysis was performed after the completion of the Michael addition. Crude **3a** was subjected to the oxidation without purification.

Further optimization was achieved through acceleration of the reaction with cinchona alkaloid-derived primary amines, which have been widely used as amenable chiral catalysts.[22] While γ-keto ester **4a** was obtained with inferior *er* by the introduction of primary amine catalysts,

the Michael addition was complete within 48 h at a concentration of 0.5 M (Entries 8-11, Table 1). Notably, the present Michael addition-oxidative methanolysis approach could also be achieved in a one-pot fashion. After removal of the solvent in the Michael reaction, **4a** was obtained in moderate yield via the direct oxidative methanolysis of **3a**; thus streamlining the protocol. Despite the fact that excess **2a** was oxidized to 1,3-diphenyl-2,3-epoxy-1-propanone as a by-product, it could be easily separated from **4a** via SiO₂ column chromatography. It was also found that different primary amines afforded **4a** with similar levels of stereoselectivity.

Table 2. One-Pot Synthesis of α-Stereogenic γ-Keto Esters Catalyzed by Primary Amines.

		solvent = CH₂Cl₂		
entry	catalyst	additive	yield (%)[a]	er of 4a[b]
1	CN-2	PhSO₃H·H₂O	53	90:10
2	CN-2	CF₃SO₃H	54	86:14
3	CN-2	PhCO₂H	51	81:19
4	CN-2	CH₃CO₂H	56	82:18
5	CN-2	ClCH₂CO₂H	55	88:12
6	CN-2	Cl₂CHCO₂H	54	94:6
7	CN-2	Cl₃CCO₂H	56	95:5
8	CN-2	CF₃CO₂H	51	92:8
9	CN-2	ClCH₂CO₂H (20 mol %)	35	89:11
10	CN-2	ClCH₂CO₂H (50 mol %)	8	90:10
11	QD-2	CH₃CO₂H	62	87:13
12	QD-2	ClCH₂CO₂H	61	92:8
13	QD-2	Cl₂CHCO₂H	61	96:4
14	QD-2	Cl₃CCO₂H	65	95:5
15	QD-2	CF₃CO₂H	62	95:5

	catalyst = QD-2, additive = HCCl₂CO₂H		
entry	solvent	yield (%)[a]	er of 4a[b]
16	CH₂Cl₂	61	96:4
17	CHCl₃	53	88:12
18	CCl₄	51	86:14
19	ClC₂H₄Cl	53	95:5
20	PhCH₃	32	90:10
21	Xylenes	12	86:14
22	MeOH	54	82:18
23	EtOH	56	94:6
24	iPrOH	55	77:13
25	Et₂O	26	92:17
26	THF	51	96:4
27	DMF	2	-
28	DMSO	0	-
29	EtOAc	59	95:5

[a] Isolated yields; [b] measured by chiral HPLC.

It has been demonstrated that Brønsted acids can facilitate amine-catalyzed reactions by means of iminium activation[23] or mediating H-bonding interactions.[24] On this basis, we surmised that Brønsted acids might also be effective co-catalysts. Although initial attempts to exploit phenols and fluorinated alcohols as additives were

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unsuccessful (See SI for details), benzenesulfonic acid monohydrate brought a rather promising result (Entry 1, Table 2), indicating the importance of additive acid strength. However, the excessive acidity of CF_3SO_3H was found to have a detrimental impact on the stereoselectivity (Entry 2, Table 2). Based on these results, a series of carboxylic acids with moderate acidities was further screened.

The *er* of the reaction gradually increased as the acid strength of the additive increased (Entries 4-7, Table 2). Excellent stereoselectivity was obtained via the employment of trichloroacetic acid. Presumably, such a trend can be rationalized by strong acidity facilitating the iminium catalysis pathway more efficiently than weak acidity. Meanwhile, by decreasing the concentration of free primary amines, enhanced acidity also suppressed the less stereoselective reaction pathway mediated by neutral primary amines (Entry 9, Table 1). Similar to triflic acid, the high acidity of CF_3CO_2H also impaired the stereoselectivity of the reaction (Entries 8, Table 2). Although increasing the amount of $ClCH_2CO_2H$ did slightly enhance the *er*, this led to dramatic decreases in reaction yields (Entries 5, 9, and 10, Figure 1). Further screening of catalysts showed **QD-2** to be a superior catalyst over **CN-2**. Under the catalysis of **QD-2**, the solvent effects on the stereoselectivity were also investigated, which revealed THF to be the optimal solvent (Entry 26, Table 2). The optimized reaction conditions were eventually achieved using 10 mol % of **QD-2** as the catalyst along with 10 mol % of Cl_2CHCO_2H (DCA) in THF (Entry 26, Table 2).

**Figure 1.** Investigation of Substrate Scope.
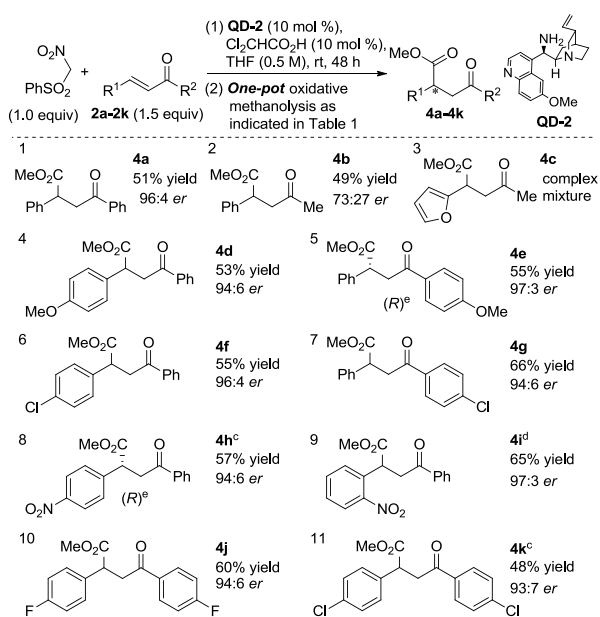
^{a} Isolated yields; ^{b} major:minor, measured by chiral HPLC; ^{c} performed in THF-CH_2Cl_2 (1:2, v:v) due to the low solubilities of enones in THF; ^{d} performed in CH_2Cl_2 due to the low solubilities of the enone in THF; ^{e} the absolute configuration determined by X-ray crystallography, see SI.

As outlined in Figure 1, various enones were investigated in the one-pot Michael addition-oxidative methanolysis protocol. In general, both electron-rich and electron-deficient chalcone derivatives underwent the reaction smoothly, affording α-stereogenic γ-keto esters in moderate yields with high enantiomeric selectivities (Entries 1 and 4-11, Figure 1). Similar to the previous reaction using fluorinated pronucleophile,[16a] the present reaction has also demonstrated *R*-facial discrimination on the α carbon. However, when 4-(2-furyl)-3-buten-2-one was subjected to the reaction, only a complex mixture was obtained, possibly due to the lability of the furan ring under the oxidation conditions (Entry 3, Table 4).[25] Although methyl styryl ketone participated in the reaction, the *er* was found to be rather low, indicating the limitation of the present protocol (Entry 2, Figure 1).

To demonstrate the synthetic utility of the present protocol, **4i** was subjected to a tandem reduction-reductive amination reaction.[26] As depicted in Scheme 3, synthetically useful tetrahydroquinoline-4-carboxylic ester **5** was obtained as a single diastereomer in good yield without significant loss of optical purity.[27]

Scheme 4. Stereoselective Synthesis of Tetrahydropyridine
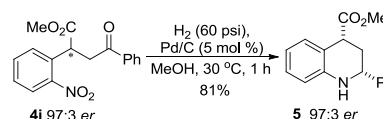
In summary, a feasible protocol has been achieved for the enantioselective preparation of α-stereogenic γ-keto esters via an umpolung strategy. Exploiting nitro(phenylsulfonyl)methane (NSM) as an acyl anion precursor, various γ-keto esters were obtained in moderate yields with good enantioselectivities. The large-scale preparation of NSM has also been achieved, making the protocol operationally simple. In particular, the protocol is significantly streamlined by merging the asymmetric organocatalyzed Michael addition and the subsequent oxidative methanolysis into a one-pot reaction. Further investigation of NSM as an acyl anion equivalent in the Mannich reaction is currently underway in our laboratory.

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