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Enantioselective formation of quaternary stereocenters using the catalytic intramolecular Stetter reaction

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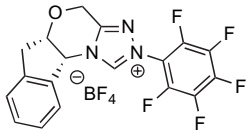
Abstract—Asymmetric formation of quaternary stereocenters has been accomplished using the catalytic intramolecular Stetter reaction. A variety of tethered aldehydes and Michael acceptors are cyclized in excellent yields and enantioselectivities.

1. Introduction

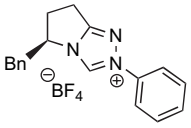
Catalytic carbon–carbon bond formation resulting in the creation of a quaternary stereocenter is a useful but challenging tool in organic chemistry.[1] In addition to established approaches using chiral auxiliaries,[2] significant progress has been made in recent years aimed at catalytic methods for the formation of quaternary stereocenters. These include the intramolecular Heck reaction,[3] rearrangement of enol carbonates,[4] transition metal-mediated π-allyl chemistry,[5] copper catalyzed S_N2' displacement of allylic leaving groups[6] and conjugate additions of β-keto esters to acrylates,[1b] phase-transfer alkylation of 1-indanones,[7] arylation of ketone enolates,[8] and enantioselective alkylation of tributyl tin enolates catalyzed by Cr(salen)Cl,[9] among others. Most recently, Stoltz and Trost have each reported the deracemization of quaternary stereocenters via Pd-catalyzed decarboxylative allylation of racemic β-keto esters.[10,11] Each of these approaches is useful but limited to a specific substrate scope.

Reactivity umpolung reverses the normal mode of aldehyde polarity, thus rendering an aldehyde nucleophilic.[12] Both benzoin and Stetter reactions exploit this reactivity and have been the subject of much recent research.[13] Both processes are catalyzed by azolium salts in the presence of base.[14] The benzoin reaction provides α-hydroxy ketones and has classically been limited to the homocoupling of two aldehydes.[15] Recently, creative approaches have been taken to expand its utility to provide cross-benzoin products.[16] The Stetter reaction, on the other hand, involves the addition of an aldehyde to a Michael acceptor and is an excellent way to access 1,4-dicarbonyl systems.[17]

Work in our laboratory has focused on the development of chiral triazolinylidene carbenes, derived from **1** and **2**.[18] These catalysts are capable of inducing addition of aromatic and aliphatic aldehydes to α,β-unsaturated esters, ketones, and nitriles.[18a,b] Recent work includes the extension of intramolecular Stetter reaction for the formation of contiguous stereocenters using α,β-disubstituted Michael acceptors[18d] and the desymmetrization of cyclohexadienones.[18f] We have previously communicated the formation of quaternary stereocenters using β,β-disubstituted Michael acceptors.[18c] Herein, we describe an expansion of the scope of this reaction to include a variety of heteroatoms tethering the aldehyde and Michael acceptor as well as the generation of five- and six-membered rings in the process of forming quaternary stereocenters in high enantioselectivity.



1c



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2. Results and discussion

Investigation of the formation of quaternary stereocenters began with substrates such as **3**. Substrates were prepared via phenol alkylation of the thioacetal of salicylaldehyde, followed by deprotection. A brief catalyst screen provided reaction conditions that afforded excellent yields and enantioselectivities of benzofuranone products (Eq. 1). Reaction of electron rich *para*-methoxy phenyl substituted aminoindanol-derived catalyst with **3** provides **5** in 45% yield and excellent enantiomeric excess. Catalyst **1b** provides an increase in yield and retains 99% ee. Pentafluorophenyl substituted catalyst **1c** proved to be the most efficient in terms of yield and enantioselectivity.

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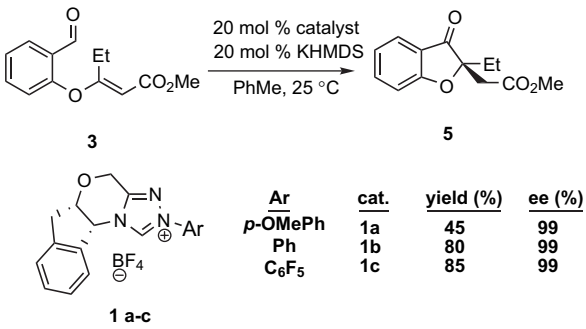
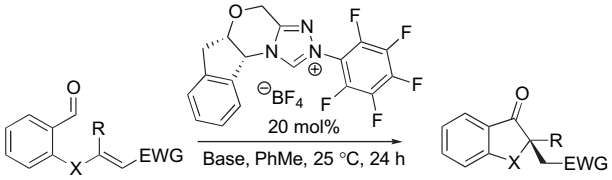


Using catalyst precursor **1c**, we further optimized the reaction conditions by using the very mild base triethylamine to generate the active catalyst. Having identified an efficient catalyst system providing desired reactivity with excellent enantioselectivity and yield, we examined the scope of this reaction beginning with substrates that contained aromatic backbones (Table 1). Benzofuranones **5** and **6** were obtained in high yields and enantiomeric excess. Thioethers are also competent substrates and react efficiently to provide benzothiophenone products in high yield and enantioselectivity (Entries 4 and 5). Reaction of thioether **7** provides benzothiophenone in 95% yield and 92% ee. A propyl group in the β-position is tolerated, providing 54% yield and 87% ee with triethylamine (Entry 4). Phenethyl substitution of the thioether substrate affords **12** in lower yield and 88% ee. A direct comparison between substrates **7** and **13** leads to the conclusion that an increase in steric bulk or electronic differences, i.e., ethyl versus phenyl, suppresses the reactivity while having little effect on enantioselectivity. An all carbon five-membered ring is formed in 95% yield and 99% ee (Entry 7). Overall, the intramolecular Stetter reaction tolerates aromatic aldehydes with varied β,β-substitution of the Michael acceptors and heteroatom tethers.

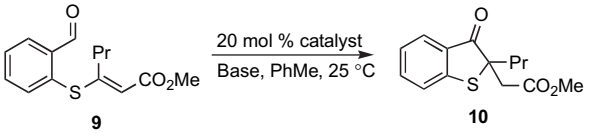
Table 1. Scope of aromatic substrates



Entry	Substrate	Product[a]	Base	Yield (%)	ee (%)[b]
1	X = H **3**	X = H **5**	NEt_3	96	97
2	= Br **4**	= Br **6**	NEt_3	92	89
3[c]	**7**	**8**	NEt_3 KO*t*-Bu	95 90	92 97
4	**9**	**10**	NEt_3 KO*t*-Bu	54 83	87 98
5	**11**	**12**	NEt_3 KO*t*-Bu	33 91	88 99
6	**13**	**14**	NEt_3 KO*t*-Bu	11 15	82 82
7	**15**	**16**	NEt_3	95	99

[a] Absolute configuration assigned analogy to **8**.
[b] Enantiomeric excess determined by HPLC analysis on chiral stationary phase.
[c] Absolute configuration established by single-crystal X-ray analysis.

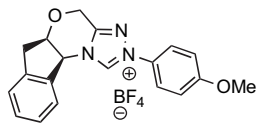
The observation that sulfur containing compounds generally provide cyclized products in lower yields and more moderate enantioselectivities prompted an additional screen of reaction conditions. This catalyst screen was performed using thioether **9**, which contains propyl substitution β to the ester. As expected, we found that aminoindanol catalyst **1c** and phenylalanine-derived catalyst **2** afford opposite enantiomers of the desired product in high selectivity (Eq. 2). Exposing **9** to catalyst **2** provides **10** in similar yield with an increase in enantioselectivity to 90%. Catalyst **1c** was then used with triethylamine but gave **10** in only moderate yield and selectivity. By changing the base to potassium *tert*-butoxide, an increase in yield and enantioselectivity was observed. The reaction conditions for thioether containing substrates were found to be 20 mol % catalyst loading, with 20 mol % potassium *tert*-butoxide, in toluene at 25 °C. Increased yields and enantioselectivities were obtained with potassium *tert*-butoxide in each sulfur containing substrate with the exception of **13**. A slight increase in reactivity was observed with **13** while the enantioselectivity remains 82%. We ascribe the reluctance of this substrate to participate in this reaction to steric crowding.



9 **10** (2)

cat.	base	yield (%)	ee (%)
2	KHMDS	80	90(S)
1c	NEt_3	54	87(R)
1c	KO*t*-Bu	83	98(R)

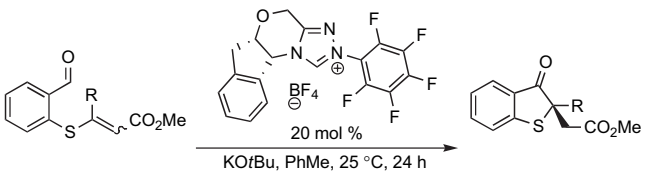
To further investigate the requirements of substrates that give high yield and enantioselectivity we synthesized both alkene isomers of the Michael acceptors. The use of either (*E*)- or (*Z*)-isomer results in good yields and enantioselectivities. Thioether *E*-**7** gives cyclized benzothiophenone in 90% yield and 97% ee. The corresponding *Z*-**7** gives **8** in 89% yield and 86% ee under the same reaction conditions. Highly electrophilic bis-ester **18** was obtained in the (*Z*)-geometry and provided cyclized product **19** in 85% yield and 90% ee when using catalyst **17**. Similar yields and lower enantioselectivities were also observed for the (*E*)-isomer of propyl- and phenethyl-substituted Michael acceptors. Use of (*E*)-isomers provided uniformly higher yields and enantioselectivities and provided the impetus for us to focus on (*E*)-isomers for the majority of the study (Table 2).



17

Although, the formation of five-membered rings and concomitant creation of quaternary stereocenters are very efficient, formation of the corresponding six-membered rings remains a challenge. Treatment of thioether **20** under the standard reaction conditions (20 mol % azolium salt and 20 mol % KHMDS in toluene) with achiral catalyst **22** affords cyclized product in 11% yield (Eq. 3). Exposure of

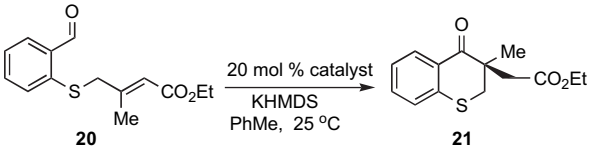
Table 2. Effect of substrate geometry



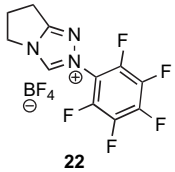
Entry	Substrate	Product	
1	*E*-**7**	**8**	(*E*) 90% yield, 97% ee
	Z-**7**		(*Z*) 89% yield, 86% ee
2	*E*-**9**	**10**	(*E*) 83% yield, 98% ee
	Z-**9**		(*Z*) 85% yield, 89% ee
3	*E*-**11**	**12**	(*E*) 91% yield, 99% ee
	Z-**11**		(*Z*) 92% yield, 84% ee
4	**18**	**19**	(*Z*) 85% yield, 90% ee[a]

[a] Results with catalyst **17** and KHMDS.

20 to the same reaction conditions with chiral catalyst **1c** provides no desired product and only the starting material was recovered. After investigating our most reactive catalysts, we found that catalyst **2** provides **21** in 11% yield and >99% ee. As we have noted a higher reactivity associated with ketones versus esters, we decided to investigate the six-membered ring formation utilizing a ketone Michael acceptor. In the event, exposure of methyl ketone **23** containing phenyl substitution to our reaction conditions provides the desired product in 55% yield and 99% ee (Eq. 4).

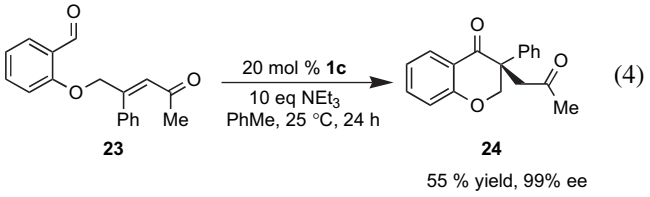


20 **21** (3)



22

cat.	yield (%)	ee (%)
22	11	-
1c	0	-
2	11	>99

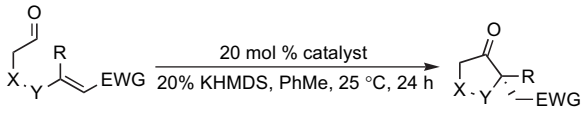


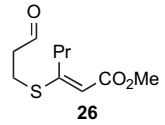
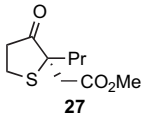
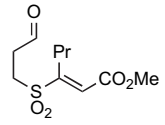
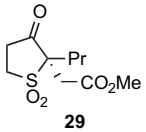
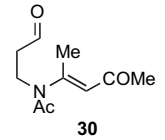
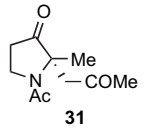
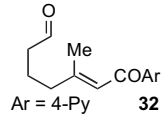
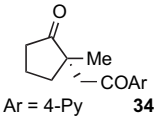
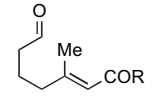
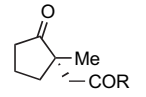
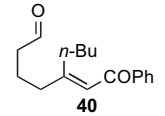
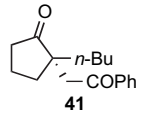
(4)

This method can be extended to substrates with aliphatic backbones, although the aliphatic substrates pose a particular challenge, as they may undergo aldol side reactions. Cyclization of aliphatic substrates to form tertiary stereocenters has been previously reported.[18a] Enantioselectivity when using substrates with aliphatic backbones is affected by the geometry of the alkene in the starting material, as is the case in earlier aromatic substrates. Optimized reaction conditions for aliphatic substrates were found to be 20 mol % catalyst and 20 mol % KHMDS in toluene. Subjecting *E*-**25** to the reaction conditions with catalyst **1c** gives cyclopentanone in 85% yield and 96% ee (Eq. 5). Cyclization proceeds in lower yield and enantioselectivity for *Z*-**25**.

(5)

Table 3. Substrate scope of aliphatic



Entry	Substrate	Product[a]	Catalyst	Yield (%)	ee (%)
1	 **26**	 **27**	**1c**, **2**	0	—
2	 **28**	 **29**	**2**	98	80[b]
3	 **30**	 **31**	**1**	65	95
4	 Ar = 4-Py **32**	 Ar = 4-Py **34**	**1**	85	96
5	=*p*-NO_2Ph **33**	=*p*-NO_2Ph **35**	**1**	90	84
6	 R = Me **36**	 R = Me **38**	**1**	81	95
7	= $(CH_2)_2$Ph **37**	= $(CH_2)_2$Ph **39**	**1**	63	99
8	 **40**	 **41**	**1**	71	98

[a] Absolute configuration assigned analogy to **37**.
[b] Enantioselectivity was determined by ^{1}H NMR using chiral shift reagent Eu(hfbc)$_3$.

Aliphatic substrates containing thioethers have also proven resistant to cyclization with catalyst **1** or **2** (Table 3). By changing the tether from a sulfide to a sulfone, cyclization was induced, providing the product in 98% yield and 80% ee. Thorpe–Ingold effect[19] may account for the success of this reaction. In addition, the electron withdrawing capability of the sulfone presumably contributes to the activation of the electron deficient alkene, thus promoting cyclization. The scope of aliphatic substrates includes nitrogen-containing substrates such as **30** that provides desired product in 65% yield and 95% ee. α,β-Unsaturated aromatic ketones **32** and **33** give the desired product in higher yields and enantioselectivities. Excellent selectivity was observed for the formation of quaternary stereocenters in **38** and **39** implementing aliphatic ketone Michael acceptors. Cyclization of α,β-unsaturated phenyl ketone **40** provided **41** in 98% ee. Aliphatic substrates with β-methyl substitution generally give high enantioselectivity.

We have expanded the scope of the intramolecular enantioselective Stetter reaction to afford quaternary stereocenters. The reaction is mild, general, and tolerates aromatic, aliphatic, sulfur, oxygen, and nitrogen tethering of aldehyde and Michael acceptor. The current substrate scope includes compounds with varying electronics and sterics. Ongoing efforts include elucidating the mechanism of this reaction and other factors contributing to the reactivity of these carbenes.

3. Experimental

3.1. General

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Data are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard (tetramethylsilane [TMS] or deuterated chloroform [$CDCl_3$]), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br s=broad singlet), integration, and coupling constant (Hz). Chemical shifts are reported in parts per million from ($CDCl_3$) taken as 77.0 ppm.

3.2. Synthesis and characterization

3.2.1. General procedure for the asymmetric intramolecular Stetter reaction of aromatic substrates. A flame-dried round bottom flask was charged with triazolium salt (0.02 mmol, 0.2 equiv), evacuated for 5 min, and then covered with argon. Substrate (0.1 mmol, 1 equiv) in toluene (1 mL) was added via syringe, followed by the addition of KO*t*-Bu (0.2 mmol, 2 equiv to substrate), and the solution was stirred at ambient temperature under argon for 24 h.

The reaction mixture was then poured onto a column of silica gel and eluted with a suitable solution of ethyl acetate in hexanes to afford analytically pure product.

3.2.2. General procedure for the asymmetric intramolecular Stetter reaction of aliphatic substrates. A flame-dried round bottom flask was charged with triazolium salt (0.02 mmol, 0.2 equiv) and toluene (1 mL) under argon. To this solution was added KHMDS (0.5 M in toluene) (0.02 mmol, 0.2 equiv) via syringe and the solution was stirred at ambient temperature for 5 min. Substrate (0.01 mmol, 1 equiv) in toluene was added (1 mL) via syringe and allowed to stir for 24 h at ambient temperature. The reaction mixture was then poured onto a column of silica gel and eluted with a suitable solution of ethyl acetate in hexanes to afford analytically pure product.

3.2.2.1. (*R*)-(3-Oxo-2-propyl-2,3-dihydro-benzo[*b*]thiophen-2-yl)-acetic acid methyl ester (10). R_f=0.43 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ +21.2 ($CHCl_3$); HPLC analysis—Chiracel OD-H column, 90:10 hexanes to isopropanol 0.5 mL/min. Minor enantiomer: 6.0 min, major enantiomer: 7.5 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 1H, J=7.7 Hz), 7.53 (t, 1H, J=7.9 Hz), 7.37 (d, 1H, J=7.9 Hz), 7.2 (t, 1H, J=7.0 Hz), 3.56 (s, 3H), 3.07 (d, 1H, J=16.7), 2.96 (d, 1H, J=16.7 Hz), 1.86 (ddd, 2H, J=5.5, 6.8, 9.6 Hz), 1.54–1.35 (m, 1H), 1.26–1.03 (m, 1H), 0.84 (t, 3H, J=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 170.4, 152.1, 135.7, 131.3, 126.8, 124.9, 124.1, 62.7, 52.0, 42.8, 41.3, 17.9, 14.1; IR (NaCl, neat) 2958, 1741, 1699, 1591, 1449 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{17}O_3S$: 265.0898. Found: 265.0885.

3.2.2.2. (*R*)-(3-Oxo-2-phenethyl-2,3-dihydro-benzo-[*b*]thiophen-2-yl)-acetic acid methyl ester (12). R_f=0.46 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ −27.8 ($CHCl_3$); HPLC analysis—Chiracel OD-H column, 90:10 hexanes to isopropanol 0.5 mL/min. Minor enantiomer: 9.3 min, major enantiomer: 11.8 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, 1H, J=7.8 Hz), 7.57 (t, 1H, J=6.9 Hz), 7.43 (d, 1H, J=7.9 Hz), 7.26–7.10 (m, 6H), 3.59 (s, 3H), 3.12 (d, 1H, J=16.8 Hz), 3.00 (d, 1H, J=16.8 Hz), 2.79–2.67 (m, 1H), 2.47–2.37 (m, 1H), 2.27–2.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 170.3, 152.0, 140.92, 136.0, 131.3, 128.6, 126.9, 126.3, 125.1, 124.3, 62.6, 52.2, 43.1, 41.2, 31.0; IR (NaCl, neat) 2950, 1741, 1699, 1591, 1450 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{19}O_3S$: 327.1055. Found: 327.1048.

3.2.2.3. (*R*)-(3-Oxo-2-phenyl-2,3-dihydro-benzo[*b*]-thiophen-2-yl)-acetic acid methyl ester (14). R_f=0.46 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ −10.3 ($CHCl_3$); HPLC analysis—Chiracel OD-H column, 90:10 hexanes to isopropanol 0.5 mL/min. Minor enantiomer: 8.4 min, major enantiomer: 6.7 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, 1H, J=7.9 Hz), 7.44 (t, 2H, J=8.1 Hz), 7.23–7.11 (m, 6H), 3.73 (s, 3H), 3.63 (d, 1H, J=14.0 Hz), 3.56 (d, 1H, J=14.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 169.6, 151.6, 136.1, 134.2, 130.9, 130.1, 128.0, 127.4, 127.2, 125.3, 123.9, 64.6, 53.7, 39.9; IR (NaCl, neat) 2952, 1738, 1699, 1589, 1450 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{15}O_3S$: 299.0742. Found: 299.0739.

3.2.2.4. 2-Methoxycarbonylmethyl-3-oxo-2,3-dihydro-benzo[*b*]thiophene-2-carboxylic acid methyl ester (19). R_f=0.36 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ +20.6 ($CHCl_3$); HPLC analysis—Chiracel AD-H column, 97:3 hexanes to isopropanol 1.0 mL/min. Minor enantiomer: 20.0 min, major enantiomer: 22.7 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, 1H, J=7.9 Hz), 7.58 (t, 1H, J=8.1 Hz), 7.40 (d, 1H, J=8.1 Hz), 7.25 (m, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 3.53 (d, 1H, J=17.3 Hz), 3.11 (d, 1H, J=17.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 170.3, 168.5, 151.9, 136.3, 129.7, 127.7, 125.7, 124.1, 62.4, 53.9, 52.4, 39.7; IR (NaCl, neat) 2954, 1738, 1705, 1587 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{13}O_5S$: 281.0484. Found: 281.0480.

3.2.2.5. (*R*)-(3-Methyl-4-oxo-thiochroman-3-yl)-acetic acid methyl ester (21). R_f=0.38 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ +41.6 ($CHCl_3$); HPLC analysis—Chiracel OD-H column, 90:10 hexanes to isopropanol 0.5 mL/min. Minor enantiomer: 8.8 min, major enantiomer: 7.5 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, 1H, J=8.6 Hz), 7.36 (t, 1H, J=6.5 Hz), 7.25–7.14 (m, 2H), 4.13 (d, 1H, J=7.1 Hz), 4.11 (q, 2H, J=7.1 Hz), 3.74 (d, 1H, J=13.5 Hz), 3.01 (d, 1H, J=16.1 Hz), 2.98 (d, 1H, J=13.5 Hz), 2.56 (d, 1H, J=16.1 Hz), 1.40 (s, 3H), 1.23 (t, 3H, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 171.2, 141.4, 133.2, 130.6, 130.0, 127.5, 125.2, 60.8, 43.6, 41.2, 36.6, 21.2, 14.4; IR (NaCl, neat) 2978, 1732, 1676, 1589, 1435 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{17}O_3S$: 265.0898. Found: 265.0905.

3.2.2.6. (1,1,3,-Trioxo-2-propyl-tetrahydro-1,6-thiophene-yl)-acetic acid methyl ester (29). R_f=0.15 (7:3 Hex/EtOAc); $[\alpha]_D^{25}$ +24.5 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.65 (ddd, 1H, J=12.5, 11.7, 8.5 Hz), 3.50 (ddd, 1H, J=12.5, 9.2, 2.4 Hz), 3.17 (d, 1H, J=17.9 Hz), 3.11 (ddd, 1H, J=17.9, 8.5, 2.2 Hz), 3.10 (d, 1H, J=17.9 Hz), 2.88 (ddd, 1H, J=17.9, 11.6, 9.1 Hz), 1.87 (ddd, 1H, J=14.1, 9.3, 7.1 Hz), 1.70 (dm, 1H, J=14.1 Hz), 1.48 (ddq, 2H, J=9.3, 7.1, 7.1 Hz), 0.93 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 171.4, 65.8, 52.8, 50.7, 39.4, 36.7, 36.3, 17.7, 14.4; IR (NaCl, neat) 2964, 1732, 1439, 1313 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{16}O_5S$: 248.0718. Found: 248.0705.

3.2.2.7. 1-Acetyl-2-methyl-(2-oxo-propyl)-pyrrolidin-3-one (31). R_f=0.21 (9:1 EtOAc/*i*-PrOH); $[\alpha]_D^{25}$ −57.1 ($CHCl_3$); GC analysis—chiraldex BPH column, 120 °C 1.5 mL/min. Minor enantiomer: 46.0 min, major enantiomer: 46.2 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (dd, 1H, J=18.6, 0 Hz), 3.82 (ddd, 1H, J=18.1, 8.9, 8.9 Hz), 3.75 (ddd, 1H, J=10.2, 10.2, 3.8 Hz), 2.96 (dd, 1H, J=18.8, 0 Hz), 2.90 (ddd, 1H, J=17.9, 9.0, 3.6 Hz), 2.66 (ddd, 1H, J=18.5, 9.4, 9.4 Hz), 2.03 (s, 3H), 2.01 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 207.3, 170.6, 64.1, 50.9, 43.9, 29.4, 23.2, 22.2; IR (NaCl, neat) 2915, 1745, 1706, 1634, 1414 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{16}NO_3$, 198.1130. Found 198.1135.

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Supplementary data

Synthesis and characterization for starting materials are provided in Supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.06.042.

References and notes

1. (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 389–401; (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363–5367; (c) *Challenges and Solutions for Organic Synthesis*; Christoffers, J., Ed.; Wiley-VCH: Weinheim, 2005.
2. (a) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843–9873; (b) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503–9569.
3. Shibasaki, M.; Vogl, E. M. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, NY, 1999; pp 475–487.
4. (a) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921–3924; (b) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368–13369.
5. Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759–6760.
6. Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456–1460.
7. Battacharya, A.; Dolling, U. H.; Grabowski, E. J. J.; Karady, S.; Ryan, K. M.; Weinstock, L. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 476–477.
8. Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918–1919.
9. Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62–63.
10. Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924–6927.
11. Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847.
12. Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239–258.
13. For reviews, see: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534–541; (b) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326–1328; (c) Pohl, M.; Lingen, B.; Müller, M. *Chem.—Eur. J.* **2002**, *8*, 5288–5295.
14. Breslow, R. J. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.
15. (a) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743–1745; (b) Enders, D.; Breuer, K. *Helv. Chim. Acta* **1996**, *79*, 1217–1221; (c) Aitken, R. A.; Thomas, A. W. Heterocyclic Acyl and Formyl Anion Equivalents. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: San Diego, CA, 2001; Vol. 79, pp 89–115; (d) Knight, R. L.; Leeper, F. J. *Tetrahedron Lett.* **1997**, *38*, 3611–3614; (e) Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891–1893; (f) Dudding, T.; Houk, K. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5770–5775; (g) Sheehan, J. C.; Hunneman, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 3666–3667.
16. (a) Linghu, X.; Bausch, C. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 1833–1840; (b) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1–6; (c) Hachisu, Y.; Bode, J. W.; Suzuki, K. *Adv. Synth. Catal.* **2004**, *346*, 1097–1100; (d) Dünnwald, T.; Demir, A. S.; Siegert, P.; Pohl, M.; Müller, M. *Eur. J. Org. Chem.* **2000**, 2161–2170.
17. (a) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639–648; (b) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407–496.
18. (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299; (b) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934–1936; (c) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876–8877; (d) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284–6289; (e) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725–5728; (f) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552–2553; (g) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, 2025–2035; (h) Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2003**, 195–197.
19. (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080–1106; (b) Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305–329.