

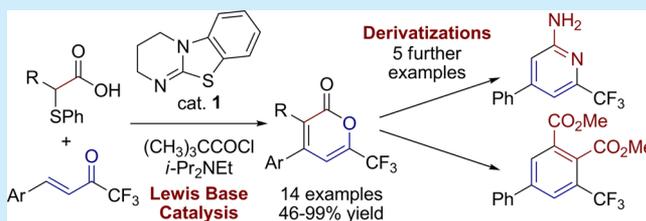
Isothiurea-Mediated One-Pot Synthesis of Trifluoromethyl Substituted 2-Pyrones

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S Supporting Information

ABSTRACT: A one-pot isothiurea-mediated Michael addition/lactonization/thiol elimination cascade sequence for the formation of 4,6-disubstituted and 3,4,6-trisubstituted 2-pyrones from (phenylthio)acetic acids and α,β -unsaturated trifluoromethyl ketones is described. The synthesis of a COX-2 inhibitor and the wide-ranging derivatization of the 2-pyrone moiety to trifluoromethyl substituted aromatics and hetero-aromatics is also disclosed.

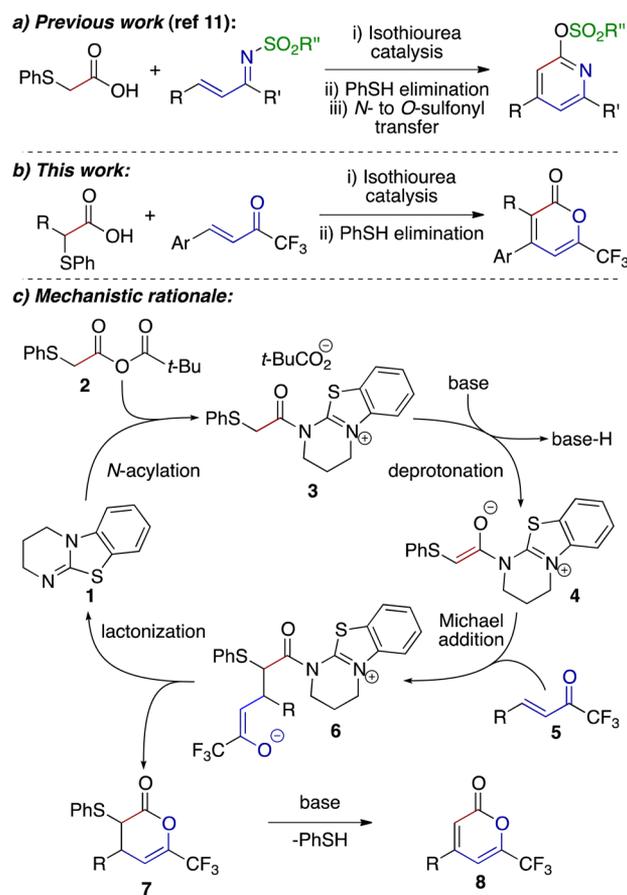


2-Pyrones are a class of unsaturated heterocycle that is extremely prevalent in Nature,¹ with examples being found in plants, animals, marine organisms, bacteria, fungi, and insects.² The parent 2-pyrone heterocycle has recently been found to have both cytotoxic and DNA-damaging effects in lung cancer cells.³ Several examples of the 2-pyrone containing bufadienolide family of bioactive natural products have been isolated from the traditional Chinese medicine Ch'an Su, underlying their potential as therapeutic agents.⁴ Alongside their biological importance, 2-pyrones have also found great utility in complex molecule synthesis. Their reactivity toward both nucleophiles and electrophiles has permitted their use in the synthesis of a wide range of highly valued heterocyclic and nonheterocyclic compounds.^{2,5} Despite their synthetic utility there are few routes to 2-pyrones, the most common being the tandem condensation/cyclization of β -ketoesters,^{2,6} and novel catalytic synthetic routes to these heterocycles are of significant interest.

Building upon the seminal work of Romo and co-workers on the *in situ* activation of carboxylic acids⁷ to generate ammonium enolates,⁸ we have demonstrated that isothiureas⁹ catalyze the intermolecular Michael addition/lactonization/lactamization of arylacetic acids and electron-deficient Michael acceptors.¹⁰ This concept was further developed by incorporating a suitable leaving group within the acetic acid,¹¹ allowing the generation of pyridines through a cascade (Michael addition/lactamization/elimination) sequence followed by *N*- to *O*-sulfonyl transfer (Scheme 1a). Seeking to further develop this concept, herein we report the successful development of an organocatalyzed synthesis of 2-pyrones, incorporating the pharmaceutically relevant trifluoromethyl substituent¹² at the 6-position (Scheme 1b).¹³

Our mechanistic rationale for this transformation begins with *N*-acylation of DHPB (3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole) **1** with mixed anhydride **2**, formed *in situ* from phenyl(thio)acetic acid, pivaloyl chloride, and a base (Scheme 1c). Deprotonation of **3** affords the (*Z*)-enolate **4**, which would undergo Michael addition to trifluoromethyl enone **5**.¹⁴ Lactonization *via* **6** forms dihydropyrone **7** with concomitant

Scheme 1. Isothiurea-Mediated One-Pot Synthesis of Planar Heterocycles



Received: December 20, 2013

Published: January 16, 2014

regeneration of DHPB, and rapid off-cycle elimination of thiophenol forms the pyrone **8**.

Initially, the reaction of *in situ* activated (phenylthio)acetic acid **9a** with trifluoromethyl enone **10** in the presence of 20 mol % DHPB **1** and excess *i*-Pr₂NEt gave the desired pyrone **11** in a promising 72% isolated yield (Table 1, entry 1).

Table 1. Reaction Optimization

entry	acid ^a	cat. (mol %)	solvent	time (h)	yield (%) ^b
1	9a	1 (20)	CH ₂ Cl ₂	72	72
2	9a	12 (20)	CH ₂ Cl ₂	24	(52) ^c
3	9a	13 (20)	CH ₂ Cl ₂	27	(34)
4	9a	1 (20)	MeCN	24	88 (99)
5	9a	13 (20)	MeCN	24	50 (55)
6 ^d	9a	1 (20)	MeCN	24	72 (84)
7 ^d	9a^e	1 (20)	MeCN	24	77
8 ^f	9a	1 (20)	MeCN	24	80
9 ^g	9a	1 (20)	MeCN	24	90
10	9a	1 (1)	MeCN	24	77
11	9a	1 (0.1)	MeCN	24	71
12	9a	— ^h	MeCN	24	59
13	9b	1 (20)	MeCN	24	24
14	9c	1 (20)	MeCN	24	23

^a2 equiv of acid **9a–c**. ^bIsolated yield; NMR yield in parentheses measured against 1-methyl naphthalene as internal standard. ^c**10** not fully consumed. ^dReaction conditions: (CH₃)₃CCOCl (2 equiv), *i*-Pr₂NEt (2 equiv), **1**, **10**, *i*-Pr₂NEt (2 equiv). ^e1.5 equiv of **9a**. ^fOpen flask conditions. ^g6 mmol of **10**, 1.30 g of pyrone **11** isolated. ^hReaction in the absence of DHPB **1**.

Alternative Lewis bases resulted in a poor conversion into **11** according to ¹H NMR analysis of the crude reaction mixtures (entries 2 and 3). The reaction solvent was next examined, with MeCN proving superior, giving **11** in 88% isolated yield (entry 4). Attempts to reduce the equivalents of pivaloyl chloride, the base, and acid **9a** or to perform the reaction under non-anhydrous conditions resulted in inferior yields of **11** (entries 6–8). The reaction was amenable to scale-up, affording 1.30 g of **1** in 90% yield from 6 mmol of acceptor **10** (entry 9). The catalyst loading could be reduced to 0.1 mol %, resulting in acceptable but lower isolated yields (entries 10 and 11). Surprisingly, a strong background reaction was observed, giving **11** in 59% isolated yield in the absence of an isothiourea catalyst, with full consumption of **10** (entry 12). However, DHPB **1** clearly promotes the desired reaction pathway leading to higher isolated yields of **11**. Chloro- and bromoacetic acid **9b** and **9c** were also screened under these conditions, but returned low yields of **11** with full consumption of acceptor **10** (entries 13 and 14).¹⁵

With optimized conditions in hand, a systematic examination of the scope of the reaction with aryl substituted trifluoromethyl enones was conducted, at both 1 and 20 mol % catalyst loadings (Table 2). Both electron-poor and -neutral

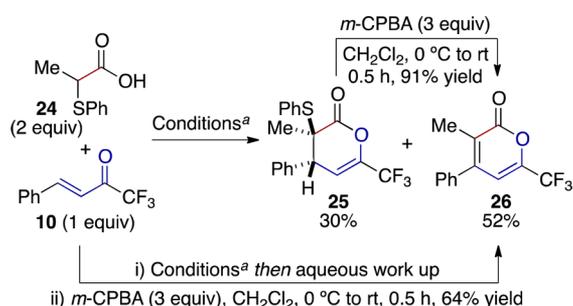
Table 2. Reaction Scope: Variation of Trifluoromethyl Enone

product	yield ^a	product	yield ^a
14	57 (95)	19	73 (95)
15	73 (95)	20	63 (82)
16	71 (88)	21	45 (83)
17	53 (85)	22	(68)
18	(61) ^b	23	89 (99)

^aIsolated yield with 1 mol % **1**; numbers in parentheses refer to isolated yield with 20 mol % **1**. ^b72 h reaction.

para-substituted aromatics were generally well tolerated, giving high yields of pyrones **14–17** at the 20 mol % loading. However, isolated yields with electron-poor aromatics were acceptable but lower at 1 mol % **1**. An extended reaction time of 72 h was required for the formation of *para*-methoxy substituted pyrone **18**, even with 20 mol % **1**. Halogen substituents at the *meta*- and *ortho*-positions (**19** and **20**) were incorporated without consequence, and heteroaromatic 2-thiophenyl and 2-furanyl substituted pyrones **21** and **22** could also be accessed in satisfactory yields. Finally, the 2-naphthalene substituted pyrone **23** was isolated in excellent yield at both 1 and 20 mol % **1**.

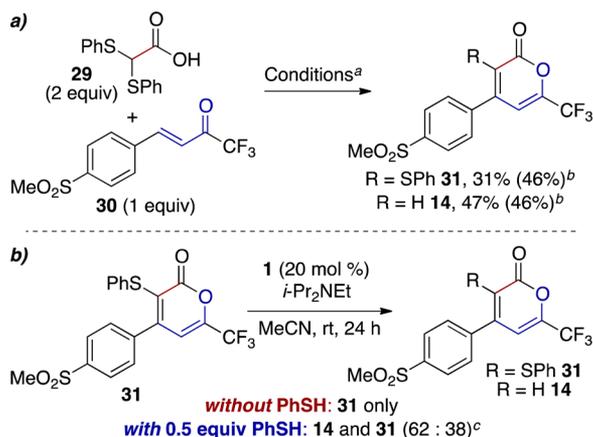
The possibility of introducing further substituents through the use of α -substituted (phenylthio)acetic acids to generate 3,4,6-trisubstituted pyrones was then investigated, as α,α -disubstituted acetic acids have proven to be a limiting factor in our previous work.^{10b} While the reaction of α -methyl acid **24** proved sluggish at rt even using 20 mol % of **1**, heating the reaction to 95 °C in a sealed tube resulted in a separable 59:41 mixture of the desired trisubstituted pyrone **26** and a single diastereoisomer of sulfide **25** that were isolated in an excellent overall yield (Scheme 2). Sulfide **25** had the expected *syn* relationship between the C(4)H and the SPh group (as confirmed by single crystal X-ray analysis), which would be unable to undergo *anti*-periplanar elimination.¹⁶ To facilitate the desired elimination, the exposure of **25** to *m*-CPBA¹⁷ delivered pyrone **26** in 91% yield, presumably through

Scheme 2. 3,4,6-Trisubstituted Pyrone from α -Methyl Acid 24

^aReaction conditions: (CH₃)₃CCOCl (3 equiv), *i*-Pr₂NEt (3 equiv), MeCN, rt, 0.5 h; then **1** (20 mol %), *i*-Pr₂NEt (2.5 equiv), Δ , 24 h.

syn-elimination of phenylsulfenic acid.¹⁸ This process could be expedited, with the oxidation carried out directly on the mixture of products isolated after aqueous workup, affording **26** in good yield. 3-Phenyl pyrone **27** could also be accessed in moderate yield.¹⁹

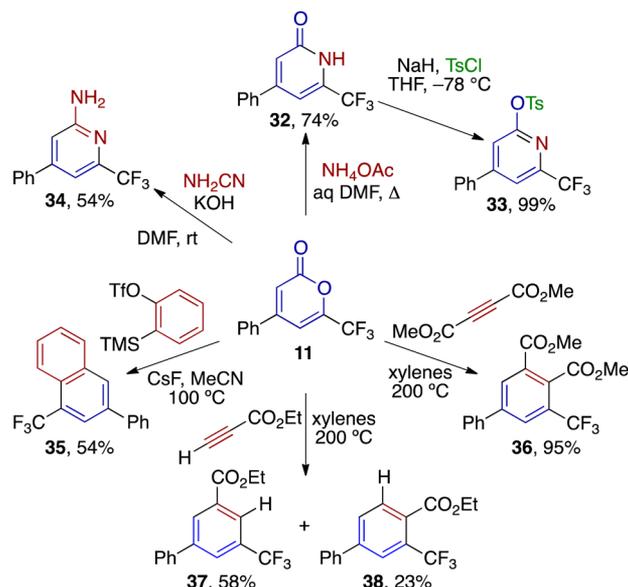
To demonstrate the viability of this methodology, its application to a suitable target with established biological activity was investigated. Merck & Co. have examined trifluoromethyl substituted pyrones as COX-2 inhibitors, with 3-phenylthio substituted pyrone **31** as a potent example (Scheme 3a).²⁰

Scheme 3. Synthesis of COX-2 Inhibitor **31**

^aReaction conditions: (CH₃)₃CCOCl (3 equiv), *i*-Pr₂NEt (3 equiv), MeCN, rt, 30 min; then **1** (1 or 20 mol %), **30**, *i*-Pr₂NEt (2.5 equiv), rt, 2 h. ^bIsolated yield with 20 mol % **1**. ^cRatio by ¹H NMR.

Bis(phenylthio)acetic acid **29**²¹ and acceptor **30** were considered viable precursors to this target, and their reaction generated a separable mixture of pyrones **31** and **14**.²² To ascertain the origin of the desulfurized byproduct **14**, control experiments were conducted upon isolated **31**. Resubmission of **31** to the reaction conditions (20 mol % **1**, *i*-Pr₂NEt, MeCN, rt) returned only starting material (Scheme 3b). However, when thiophenol was also added to this mixture, **31** was rapidly converted into desulfurized **14**, suggesting that thiophenol eliminated during the expected reaction was causing desulfurization of **31**. Attempts to suppress this undesired reaction were unsuccessful; however **31** was accessed in 32% overall yield from commercial materials.²³

Derivatization of the reactive pyrone moiety to generate additional high-value products was next investigated (Scheme 4).

Scheme 4. Derivatizations of Pyrone **11**

The reaction of **11** with ammonium acetate in aqueous DMF resulted in smooth conversion into pyridone **32**. Subsequent *O*-tosylation provided 2-tosyl pyridine **33** in excellent overall yield. This provides an alternative and high yielding three-step route to a compound synthesized in our related pyridine methodology.¹¹ Diels–Alder/retro-Diels–Alder sequences with benzyne and cyanamide gave the naphthalene and 2-amino pyridines **34** and **35**. Furthermore, employing DMAD and ethyl propiolate generated the benzene derivatives **36**–**38** in excellent yield, with the latter giving a 68:38 (**37**:**38**) mixture of regioisomers that were readily separable by flash column chromatography.

In conclusion, the concise synthesis of a range of di- and trisubstituted 2-pyrones from (thiophenyl)acetic acids and readily available trifluoromethyl enones *via* an isothioure-mediated one-pot Michael addition/lactonization/thiol elimination sequence has been demonstrated. The efficiency of this process allows the synthesis of biologically relevant compounds with high selectivity and yield. Further investigations in our laboratory are directed toward novel applications of isothiourreas in catalysis.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures, characterization data, spectra, and X-ray structure of **25**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

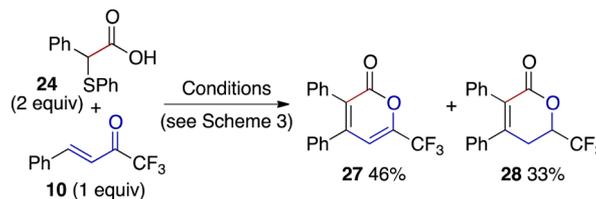
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Royal Society for a University Research Fellowship (ADS) and the EPSRC (EP/J018139/1, DSBD) for funding. We also thank the EPSRC UK National Mass Spectrometry Facility at Swansea University.

REFERENCES

- (1) For reviews of 2-pyrones in Nature, see: (a) Dickinson, J. M. *Nat. Prod. Rep.* **1993**, *10*, 71–98. (b) McGlacken, G. P.; Fairlamb, I. J. S. *Nat. Prod. Rep.* **2005**, *22*, 369–385.
- (2) For a comprehensive review of the isolation, synthesis, and reactions of 2-pyrones, see: Goel, A.; Ram, V. J. *Tetrahedron* **2009**, *65*, 7865–7913.
- (3) Calderón-Montañón, J. M.; Burgos-Morón, E.; Orta, M. L.; Pastor, N.; Austin, C. A.; Mateos, S.; López-Lázaro, M. *Toxicol. Lett.* **2013**, *222*, 64–71.
- (4) Nogawa, T.; Kamano, Y.; Yamashita, A.; Pettit, G. R. *J. Nat. Prod.* **2001**, *64*, 1148–1152.
- (5) (a) Shin, I.-J.; Choi, E.-S.; Cho, C.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2303–2305. (b) Jung, Y.-G.; Lee, S.-C.; Cho, H.-K.; Darvatkar, N. B.; Song, J.-Y.; Cho, C.-G. *Org. Lett.* **2012**, *15*, 132–135. (c) Cho, H.-K.; Lim, H.-Y.; Cho, C.-G. *Org. Lett.* **2013**, *15*, 5806–5809. (d) Sun, C.-L.; Fürstner, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 13071–13075.
- (6) Smith, N. R.; Wiley, R. H. *Org. Synth.* **1952**, *32*, 76.
- (7) (a) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945–7946. (b) Cortez, G. S.; Oh, S. H.; Romo, D. *Synthesis* **2001**, 1731–1736. (c) Oh, S. H.; Cortez, G. S.; Romo, D. *J. Org. Chem.* **2005**, *70*, 2835–2838. (d) Henry-Riyad, H.; Lee, C.; Purohit, V. C.; Romo, D. *Org. Lett.* **2006**, *8*, 4363–4366. (e) Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9*, 2143–2146. (f) Purohit, V. C.; Matla, A. S.; Romo, D. *J. Am. Chem. Soc.* **2008**, *130*, 10478–10479. (g) Nguyen, H.; Ma, G.; Romo, D. *Chem. Commun.* **2010**, *46*, 4803–4805. (h) Morris, K. A.; Arendt, K. M.; Oh, S. H.; Romo, D. *Org. Lett.* **2010**, *12*, 3764–3767. (i) Leverett, C. A.; Purohit, V. C.; Romo, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 9479–9483. (j) Nguyen, H.; Ma, G.; Gladysheva, T.; Fremgen, T.; Romo, D. *J. Org. Chem.* **2010**, *76*, 2–12. (k) Liu, G.; Romo, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 7537–7540. (l) Liu, G.; Shirley, M. E.; Romo, D. *J. Org. Chem.* **2012**, *77*, 2496–2500. (m) Leverett, C. A.; Purohit, V. C.; Johnson, A. G.; Davis, R. L.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2012**, *134*, 13348–13356.
- (8) Gaunt, M. J.; Johansson, C. C. C. *Chem. Rev.* **2007**, *107*, 5596–5605.
- (9) For a review of isothioureas in catalysis, see: (a) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109–2121. For seminal reports of isothioureas in catalysis, see: (b) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351–1354. (c) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536–6537. (d) Kobayashi, M.; Okamoto, S. *Tetrahedron Lett.* **2006**, *47*, 4347–4350.
- (10) (a) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714–2720. (b) Morrill, L. C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci.* **2012**, *3*, 2088–2093. (c) Simal, C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 3653–3657. (d) Morrill, L. C.; Douglas, J.; Lebl, T.; Slawin, A. M. Z.; Fox, D. J.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 4146–4155. (e) Belmessieri, D.; Cordes, D. B.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2013**, *15*, 3472–3475. For related methodology generating α,β -unsaturated acyl ammoniums from homoanhydrides, see: (f) Robinson, E. R. T.; Fallan, C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 2193–2200.
- (11) Stark, D. G.; Morrill, L. C.; Yeh, P.-P.; Slawin, A. M. Z.; O’Riordan, T. J. C.; Smith, A. D. *Angew. Chem., Int. Ed.* **2013**, 11642–11646.
- (12) Petrov, V. A. *Fluorinated Heterocyclic Compounds. Synthesis, Chemistry, and Applications*; Wiley: Hoboken, NJ, 2009.
- (13) For recent syntheses of 6-trifluoromethyl-2-pyrones, see: Usachev, B. I.; Obydenov, D. L.; Rösenthaller, G.-V.; Sosnovskikh, V. Y. *Org. Lett.* **2008**, *10*, 2857–2859 and references therein.
- (14) Kelly, C. B.; Mercadante, M. A.; Leadbeater, N. E. *Chem. Commun.* **2013**, *49*, 11133–11148.
- (15) (Phenylsulfinyl)-, 2-methoxy-, and 2-benzyloxyacetic acid were also tested, but all gave intractable mixtures of products.
- (16) See the Supporting Information. CCDC 974564 (**25**) 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.
- (17) Roush, W. R.; Spada, A. P. *Tetrahedron Lett.* **1983**, *24*, 3693–3696.
- (18) Resubmission of isolated sulfide **25** to the reaction conditions (DHPB **1**, *i*-Pr₂NEt, MeCN, Δ) returned only starting material.
- (19) 3-Phenyl substituted pyrone **27** was isolated along with the dihydropyrene **28**, presumably resulting from thiophenol-mediated desulfurization of the phenyl analogue of sulfide **25** and tautomerization. See the Supporting Information for details.



(20) Li, C.-S.; Lau, C. K.; Therien, M.; Prasit, P. U.S. Patent: 2002058690 A1, 2002.

(21) Kenney, W. J.; Walsh, J. A.; Davenport, D. A. *J. Am. Chem. Soc.* **1961**, *83*, 4019–4022.

(22) Ratios of **31** to **14** by crude ¹H NMR were 45:55 and 50:50 at 1 and 20 mol % respectively.

(23) See the Supporting Information for details.