Isothiourea-Catalyzed Enantioselective Functionalization of 2-Pyrrolyl Acetic acid: Two-Step Synthesis of Stereodefined Dihydroindolizinones

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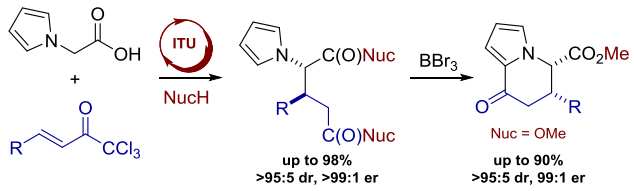
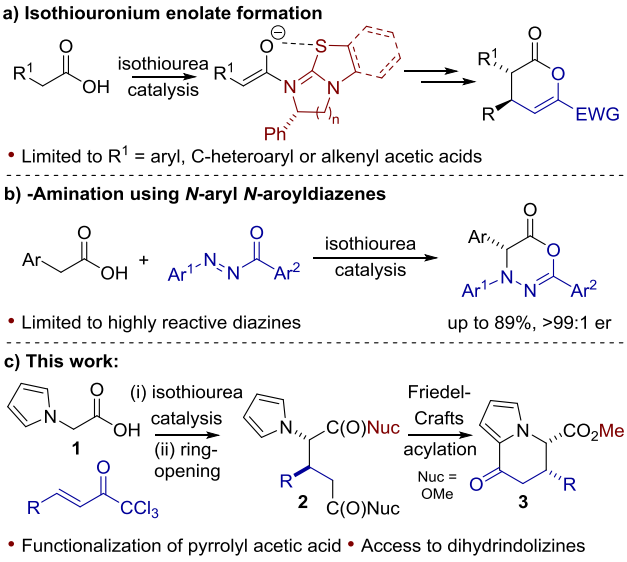
Supporting Information Placeholder



ABSTRACT: Catalytic enantioselective functionalization of 2-pyrrolyl acetic acid with trichloromethyl enones using isothiourea catalysis is reported, leading to a range of stereodefined diesters and diamides after nucleophilic ring-opening with either methanol or benzylamine (30 examples, up to >95:5 dr and >99:1 er). Subsequent intramolecular Friedel-Crafts reaction allows access to dihydroindolizinones in high yields and stereofidelity (6 examples, up to >95:5 dr and 99:1 er)

Ammonium enolates generated from carboxylic acid derivatives are versatile reactive intermediates that can be used in a variety of stereoselective bond-forming processes.[1] In this regard, isothioureas have emerged as powerful organocatalysts in a range of transformations proceeding via isothiouronium enolate intermediates.[2] For example, the stereoselective intermolecular Michael addition-lactonization/lactamization of isothiouronium enolates with suitable α,β-unsaturated enones or imines can be used to generate substituted dihydropyranones or dihydropyridinones, respectively, with excellent diastereo- and enantioselectivity.[3] However, a current limitation of this methodology is the requirement for either an aryl, heteroaryl, or alkenyl substituent to be connected at the C(2) position of the arylacetic acid, with limited heteroatom tolerance at this position (Scheme 1a). α-Nitrogenous substituents can be introduced with isothiouronium intermediates using either electrophilic *N*-acyl *N*-aroyldiazenes (Scheme 1b),[4a] or via cooperative Cu catalysis using diaziridinones.[4b] To date, direct functionalisation of a carboxylic acid with an α-nitrogenous substituent using isothiouronium enolates has yet to be reported.[5] In this manuscript, the use of the pyrroloacetic acid **1** bearing an α-*N*-pyrrole substituent as an isothiouronium enolate precursor is investigated (Scheme 1c). We envisaged that enantioselective Michael addition-lactonization with a masked α,β-unsaturated ester equivalent,[6] followed by nucleophilic ring-opening, would give **2** with high diastereo- and enantiocontrol. These products would act as valuable precursors in the preparation of functionalized dihydroindolizinones **3**, using the inherent reactivity of the pyrrole unit to promote intramolecular Friedel-Crafts acylation. The indolizine core is widely found throughout Nature,[7] while substituted dihydroindolizinones have been investigated for biological activity and used as versatile intermediates in natural product synthesis.[8]

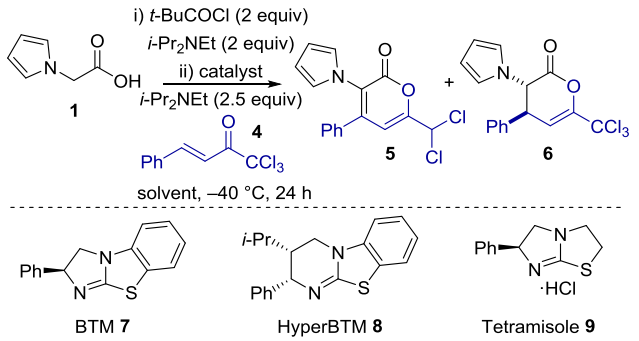
Scheme 1. Scope and limitations of isothiourea-catalyzed enolate formation from carboxylic acid oxidation level



Investigations began with the reaction of 2-(1*H*-pyrrol-1-yl)acetic acid **1** with (*E*)-1,1,1-trichloro-4-phenylbut-3-en-2-one **4** (Table 1). Treating acid **1** with pivaloyl chloride and *i*-Pr_2NEt to generate a mixed anhydride in situ, followed by addition of the isothiourea BTM **7** (10 mol%), trichloromethyl enone **4**, and further *i*-Pr_2NEt in CH_2Cl_2 at rt led to exclusive formation of the pyranone **5**, isolated in 50% yield (entry 1). The unexpected formation of **5** is thought to have arisen from

base-mediated elimination of HCl from the desired dihydropyranone **6** followed by isomerization.[9] The use of the isothiourea HyperBTM **8** as catalyst gave the first evidence of dihydropyranone **6**. However, pyranone **5** was still the major product (entry 2). Screening showed that the reaction solvent has a dramatic effect on the product distribution, with both toluene and DMF leading to preferential formation of the dihydropyranone **6**, albeit with a lower conversion of starting materials (entries 3 and 4). The use of ethyl acetate resulted in an 80% conversion into an ~12:88 mixture of **5**:**6**, with dihydropyranone **6** being formed in a promising ~89:11 dr (entry 5). Acetonitrile proved to be the optimal solvent, giving dihydropyranone **6** as the only product in ~90:10 dr with quantitative conversion of the starting materials (entry 6). The use of alternative catalysts BTM **7** and tetramisole **9** led to lower reactivity, although the product ratio and diastereoselectivity remained high (entries 7 and 8). Lowering the catalyst loading of HyperBTM **8** to 5 mol% resulted in a slight drop in product conversion (entry 9), while a control reaction in the absence of catalyst led to no product formation (entry 10). Unfortunately, all attempts to isolate product **6** by column chromatography or crystallization were unsuccessful.[10]

Table 1. Reaction optimization using pyrroloacetic acid 1

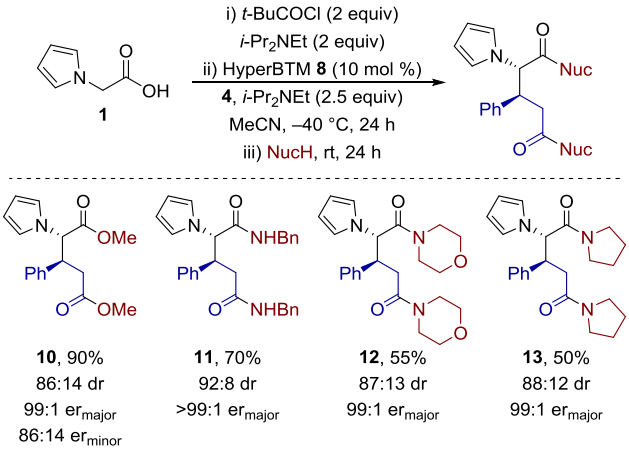


entry	**cat.** (mol %)	solvent	conv[a]	**5**:**6**[a]	**6** dr[a]
1[b]	**7** (10)	CH_2Cl_2	>99%	100:0	n/a
2	**8** (10)	CH_2Cl_2	69%	71:29	71:29
3	**8** (10)	PhMe	37%	30:70	80:20
4	**8** (10)	DMF	40%	15:85	91:9
5[c]	**8** (10)	EtOAc	80%	12:88	89:11
6	**8** (10)	MeCN	>99%	2:98	90:10
7	**7** (10)	MeCN	30%	1:99	92:8
8	**9** (10)	MeCN	49%	1:99	94:6
9	**8** (5)	MeCN	95%	3:97	88:12
10	–	MeCN	0%	n/a	n/a

[a] Determined by ^{1}H NMR analysis of crude reaction mixture. [b] Reaction performed at rt. [c] Reaction time 48 h.

To facilitate the isolation of stable derivatives of the Michael addition-lactonization product **6**, in situ ring-opening and nucleophilic displacement of the resulting CCl_3 ketone was investigated (Scheme 2). Performing the HyperBTM-catalyzed Michael addition-lactonization reaction as previously, followed by addition of excess methanol and DMAP (20 mol%) to the crude reaction mixture and warming to rt gave diester **10** as an 86:14 mixture of separable diastereoisomers isolated in 90% combined yield. Pleasingly, the major *anti*-diastereoisomer was formed in excellent 99:1 er, while the minor *syn*-diastereoisomer was obtained in 86:14 er. This process could be performed on gram-scale (8 mmol **1**) with **10** being isolated in comparable yield and enantioselectivity.[11] Ring-opening with excess benzylamine followed by aminolysis was equally successful, giving diamide **11** in 70% yield as a single diastereoisomer after purification in 99:1 er. Secondary amines such as morpholine and pyrrolidine could also be used, giving products **12** and **13** in slightly reduced yields but high er (99:1).

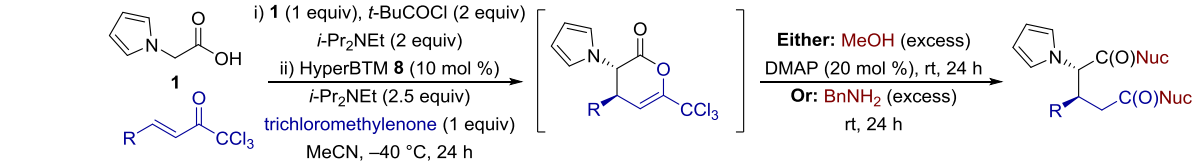
Scheme 2. Ring-opening and CCl_3 displacement[a-c]

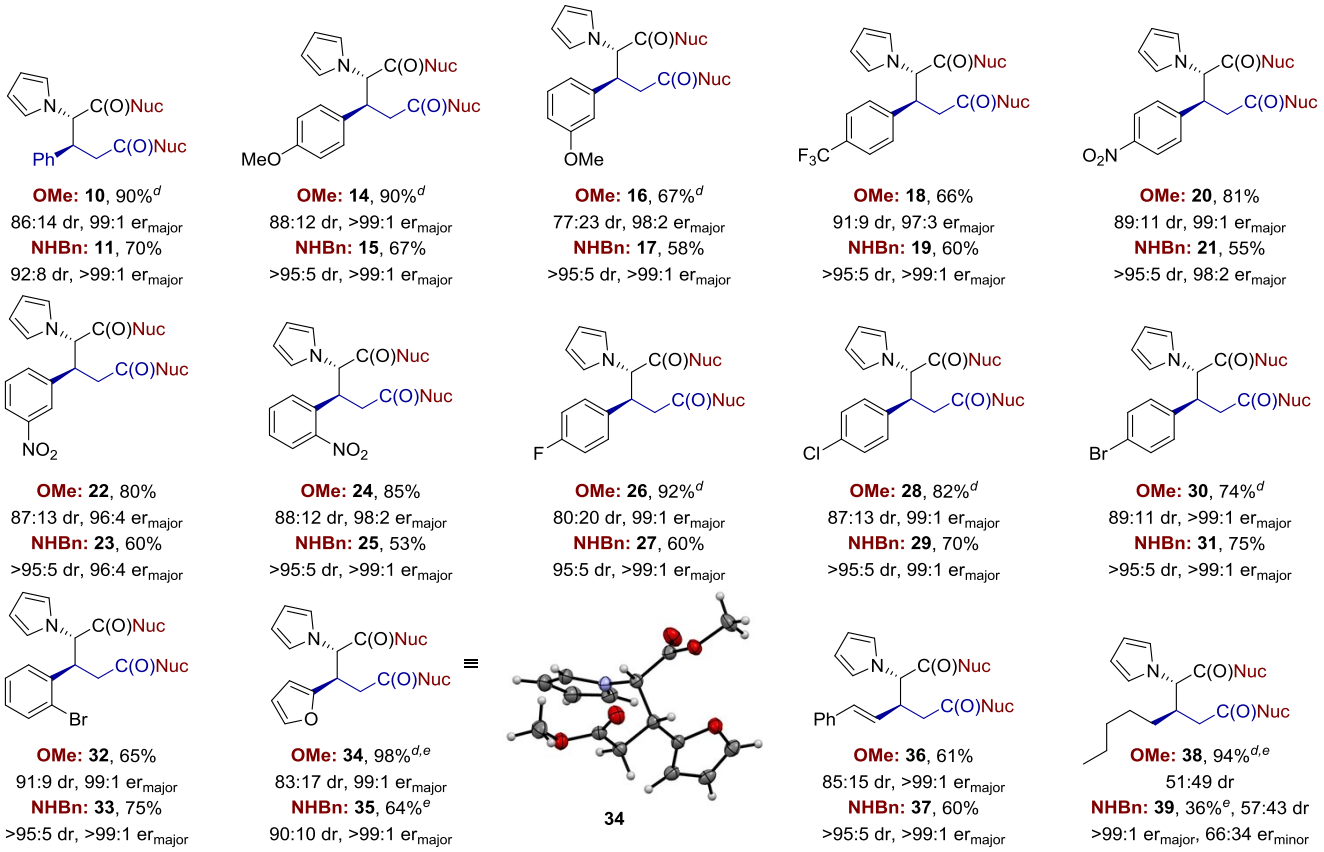


[a] dr determined by ^{1}H NMR analysis of crude reaction mixture. [b] Combined isolated yield of separable mixture of diastereoisomers. [c] er determined by HPLC analysis.

The scope of the developed methodology was further assessed by reacting pyrrole acetic acid **1** with various substituted trichloromethyl enones under the previously optimized conditions, followed by nucleophilic ring-opening and subsequent alcoholysis or aminolysis (Scheme 3). The reaction was tolerant of a range of aryl trichloromethyl enones, including those bearing electron-donating methoxy substituents, forming products **14**-**17** in good yield with excellent enantioselectivity. A range of electron-withdrawing substituents including 4-trifluoromethyl and nitro-groups in each ring-position were also well tolerated, forming products **18**-**25** without compromising the stereoselectivity. Various halogen-substituted rings were also incorporated to form products **26**-**33** in excellent yield, with the major diastereoisomer in each case being formed in 99:1 er. The use of a 2-furyl-substituted trichloromethyl enone required an extended reaction time of 40 h to form the products **34** and **35** in good yields. The major diastereoisomer of diester **34** was successfully recrystallized and single-crystal X-ray analysis provided confirmation of the relative and absolute configuration,[12] with all other products assigned by analogy. Alkenyl substituted trichloromethyl enones were also tolerated, allowing diester **36** and diamide **37** to be obtained in good yields and high er. However, alkyl-substituted trichloromethyl ketones gave products **38** and **39** obtained with low dr upon ring-opening. Notably, for each example, the diamide products resulting from aminolysis were consistently obtained with higher dr compared with the corresponding diesters from alcoholysis. Moreover, the minor diastereoisomeric diester product was obtained with lower er compared with the major diastereoisomer. For example, ring-opening with MeOH gave diesters **26**:**40** in 80:20 dr,

Scheme 3. Using pyrroloacetic acid 1 in the Michael-addition lactonization ring-opening sequence; scope and limitations[a-c]





OMe: 10, 90%[d]
86:14 dr, 99:1 er$_{major}$
NHBn: 11, 70%
92:8 dr, >99:1 er$_{major}$

OMe: 14, 90%[d]
88:12 dr, >99:1 er$_{major}$
NHBn: 15, 67%
>95:5 dr, >99:1 er$_{major}$

OMe: 16, 67%[d]
77:23 dr, 98:2 er$_{major}$
NHBn: 17, 58%
>95:5 dr, >99:1 er$_{major}$

OMe: 18, 66%
91:9 dr, 97:3 er$_{major}$
NHBn: 19, 60%
>95:5 dr, >99:1 er$_{major}$

OMe: 20, 81%
89:11 dr, 99:1 er$_{major}$
NHBn: 21, 55%
>95:5 dr, 98:2 er$_{major}$

OMe: 22, 80%
87:13 dr, 96:4 er$_{major}$
NHBn: 23, 60%
>95:5 dr, 96:4 er$_{major}$

OMe: 24, 85%
88:12 dr, 98:2 er$_{major}$
NHBn: 25, 53%
>95:5 dr, >99:1 er$_{major}$

OMe: 26, 92%[d]
80:20 dr, 99:1 er$_{major}$
NHBn: 27, 60%
95:5 dr, >99:1 er$_{major}$

OMe: 28, 82%[d]
87:13 dr, 99:1 er$_{major}$
NHBn: 29, 70%
>95:5 dr, 99:1 er$_{major}$

OMe: 30, 74%[d]
89:11 dr, >99:1 er$_{major}$
NHBn: 31, 75%
>95:5 dr, >99:1 er$_{major}$

OMe: 32, 65%
91:9 dr, 99:1 er$_{major}$
NHBn: 33, 75%
>95:5 dr, >99:1 er$_{major}$

OMe: 34, 98%[d,e]
83:17 dr, 99:1 er$_{major}$
NHBn: 35, 64%[e]
90:10 dr, >99:1 er$_{major}$

34

OMe: 36, 61%
85:15 dr, >99:1 er$_{major}$
NHBn: 37, 60%
>95:5 dr, >99:1 er$_{major}$

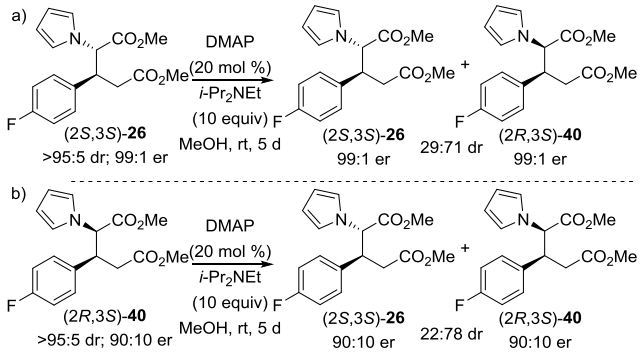
OMe: 38, 94%[d,e]
51:49 dr
NHBn: 39, 36%[e], 57:43 dr
>99:1 er$_{major}$, 66:34 er$_{minor}$

[a] Isolated yields of major diastereoisomer unless otherwise stated. [b] dr determined by ^{1}H NMR analysis of crude reaction mixture. [c] er determined by HPLC analysis. [d] Combined isolated yield of separable mixture of diastereoisomers. [e] Reaction at –40 °C for 40 h.

with purification giving the separable major (2*S*,3*S*)-diastereoisomer **26** (99:1 er), and the minor (2*R*,3*S*)-diastereoisomer **40** (90:10 er). Control experiments (Scheme 4) treated isolated (2*S*,3*S*)-**26** (>95:5 dr, 99:1 er) with DMAP (20 mol%) and excess *i*-Pr$_2$NEt in MeOH, which resulted in selective epimerization at C(2), to give a 29:71 mixture of (2*S*,3*S*)-**26** : (2*R*,3*S*)-**40**, both in 99:1 er.[13] Subjecting isolated (2*R*,3*S*)-**40** (>95:5 dr, 90:10 er) to the same conditions resulted in a similar 22:78 mixture of (2*S*,3*S*)-**26** : (2*R*,3*S*)-**40**, both in 90:10 er. These results suggest that epimerization of the major-(2*S*,3*S*)-diester diastereoisomer gives the (2*R*,3*S*)-diastereoisomer that is enantiomeric to that formed from ring-opening and alcoholysis of the minor dihydropyranone diastereoisomer from the initial Michael addition-lactonization, accounting for the lower observed product er. An analogous experiment with diamide **27** showed no epimerization, consistent with the higher dr observed for this series.[11]

Next, the synthetic utility of the diester products as dihydroindolizinone precursors was investigated (Scheme 5). Treating isolated diester **10** with boron tribromide in CH_2Cl_2 at 0 °C resulted in a facile intramolecular Friedel-Crafts acylation to form the dihydroindolizinone **41** in 75% yield without erosion

Scheme 4. Epimerization of diester products[a,b]

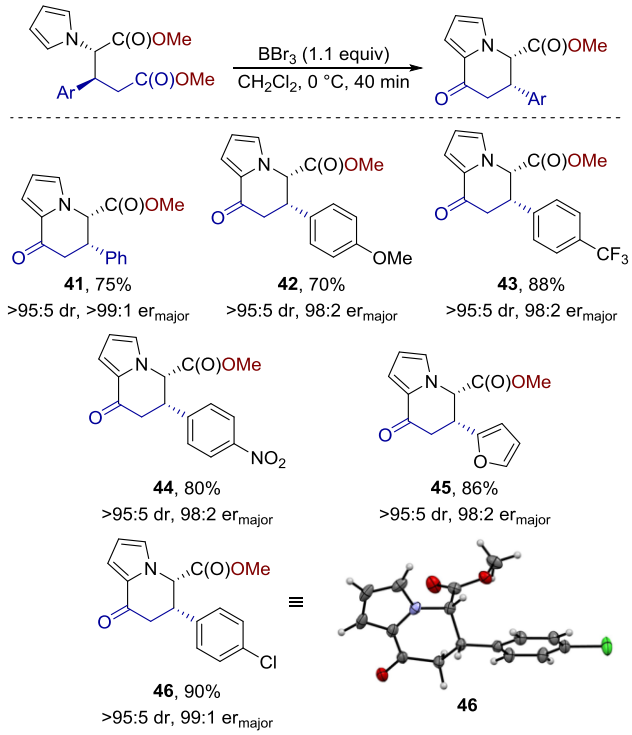


[a] dr determined by ^{1}H NMR analysis of crude reaction mixture. [b] er determined by HPLC analysis.

of either diastereo- or enantioselectivity (>95:5 dr, 99:1 er).[14] Dihydroindolizinone derivatives **42**-**44** bearing electron-donating (4-OMe) and electron-withdrawing (4-CF_3 and 4-NO_2) aryl substituents were prepared in an analogous fashion in high yield as single stereoisomers. A heteroaromatic 2-furyl

substituent was also well tolerated, forming product **45** in excellent 86% yield. Chloro-substituted dihydroindolizinone **46** was also formed in high yield, with the relative and absolute configuration confirmed by single crystal X-ray analysis.[15]

Scheme 5. Synthesis of Dihydrindolizinones [a-c]



[a] Isolated yields. [b] dr determined by ^{1}H NMR analysis of crude reaction mixture. [c] er determined by HPLC analysis.

In conclusion, 2-(1*H*-pyrrol-1-yl)acetic acid **1** is a suitable isothiouronium enolate precursor, undergoing Michael addition-lactonization with a range of α,β-unsaturated trichloromethyl enones. The dihydropyranone products readily undergo nucleophilic ring-opening followed by either alcoholysis or aminolysis to form substituted pyrroles with excellent diastereo- and enantioselectivity. These products can be further derivatized into substituted dihydroindolizinones through intramolecular Friedel-Crafts acylation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, ^{1}H and ^{13}C{^{1}H} NMR spectra, and HPLC traces for all novel compounds (PDF) Crystallographic data for **34**, **40** and **46** (CIF)

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Notes

The authors declare no competing financial interest. The research data underpinning this publication can be found at doi.org/10.17630/3ba256ef-6b22-4165-9c14-56b0357b036a

ACKNOWLEDGMENT

JET thanks The Leverhulme Trust for an Early Career Fellowship [ECF-2014-005]. ADS thanks the Royal Society for a Wolfson Research Merit Award. We also thank the EPSRC UK National Mss Spectrometry Facility at Swansea University.

REFERENCES

(1) For reviews on the reactivity of ammonium enolates, see: (a) Gaunt, M. J.; Johansson, C. C. C. *Chem. Rev.* **2007**, *107*, 5596-5605. (b) Morrill, L. C.; Smith, A. D. *Chem. Soc. Rev.* **2014**, *43*, 6214-6226.

(2) For reviews on isothiourea catalysis, see: (a) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109-2121. (b) Merad, J.; Pons, J.-M.; Chuzel, O.; Bressy, C. *Eur. J. Org. Chem.* **2016**, *2016*, 5589-5610.

(3) (a) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714-2720. (b) Simal, C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Angew. Chem. Int. Ed.* **2012**, *51*, 3653-3657. (c) Morrill, L. C.; Douglas, J.; Lebl, T.; Slawin, A. M. Z.; Fox, D. J.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 4146-4155. (d) Morrill, L. C.; Ledingham, L. A.; Couturier, J.-P.; Bickel, J.; Harper, A. D.; Fallan, C.; Smith, A. D. *Org. Biomol. Chem.* **2014**, *12*, 624-636. (e) Morrill, L. C.; Smith, S. M.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2014**, *79*, 1640-1655. (f) Smith, S. R.; Leckie, S. M.; Holmes, R.; Douglas, J.; Fallan, C.; Shapland, P.; Pryde, D.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2014**, *16*, 2506-2509. (g) Yeh, P.-P.; Daniels, D. S. B.; Fallan, C.; Gould, E.; Simal, C.; Taylor, J. E.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2015**, *13*, 2177-2191.

(4) (a) Morrill, L. C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci.* **2012**, *3*, 2088-2093. (b) Song, J.; Zhang, Z.-J.; Chen, S.-S.; Fan, T.; Gong, L.-Z. *J. Am. Chem. Soc.* **2018**, *140*, 3177-3180.

(5) Alternative methods such as organocatalytic phase-transfer catalysis using Schiff base α-glycine derivatives is an established way of forming substituted α-amino acids. For reviews, see: (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013-3028. (b) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584-4671. (c) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656-5682.

(6) (a) Zheng, C.; Li, Y.; Yang, Y.; Wang, H.; Cui, H.; Zhang, J.; Zhao, G. *Adv. Synth. Catal.* **2009**, *351*, 1685-1691. (b) Zhang, J.; Liu, X.; Ma, X.; Wang, R. *Chem. Commun.* **2013**, *49*, 9329-9331. (c) Morrill, L. C.; Stark, D. G.; Taylor, J. E.; Smith, S. R.; Squires, J. A.; D'Hollander, A. C. A.; Simal, C.; Shapland, P.; O'Riordan, T. J. C.; Smith, A. D. *Org. Biomol. Chem.* **2014**, *12*, 9016-9027. (d) Zhang, J.; Liu, X.; Wu, C.; Zhang, P.; Chen, J.; Wang, R. *Eur. J. Org. Chem.* **2014**, *2014*, 7104-7108. (e) Attaba, N.; Taylor, J. E.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2015**, *80*, 9728-9739.

(7) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139-165.

(8) (a) Dinsmore, A.; Mandy, K.; Michael, J. P. *Org. Biomol. Chem.* **2006**, *4*, 1032-1037. (b) Gracia, S.; Jerpan, R.; Pellet-Rostaing, S.; Popowycz, F.; Lemaire, M. *Tetrahedron Lett.* **2010**, *51*, 6290-6293. (c) Gerfaud, T.; Xie, C.; Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 3954-3957. (d) Gao, A. X.; Hamada, T.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 10301-10306. (e) Han, W. B.; Zhang, A. H.; Deng, X. Z.; Lei, X.; Tan, R. X. *Org. Lett.* **2016**, *18*, 1816-1819.

(9) An analogous elimination has previously been observed from *C*(3)-aryl substituted dihydropyranones, see ref. 6c.

(10) Attempted chromatographic purification of **6** presumably leads to ring-opening with water to give the corresponding diacid derivative that cannot be isolated.

(11) See the Supporting Information for details. Attempted oxidative pyrrole deprotection of **10** led to a complex mixture of products.

(12) CCDC 1853444 contains the supplementary crystallographic data for diester **34**.

(13) The relative and absolute (2*R*,3*S*)-configuration of **40** was determined by X-ray crystallographic analysis, with all other minor diastereoisomeric products assigned by analogy. CCDC 1853446 contains the supplementary crystallographic data for diester **40**.

(14) Amos, R. I. J.; Gourlay, B. S.; Molesworth, P. P.; Smith, J. A.; Sprod, O. R. *Tetrahedron* **2005**, *61*, 8226-8230.

(15) CCDC 1853445 contains the supplementary crystallographic data for dihydroindolizinone **46**.