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A Lewis acid-promoted cyclization of ethenetricarboxylate derivative aromatic compounds. Novel syntheses of oxindoles and benzofuranones *via* Friedel–Crafts intramolecular Michael addition†

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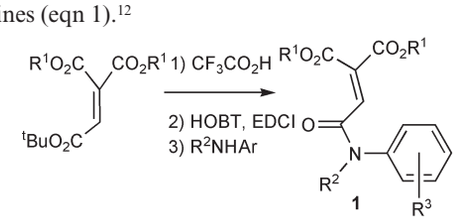
A novel cyclization reaction of ethenetricarboxylate derivative aromatic compounds in the presence of various Lewis acids gave benzo-annulated cyclic compounds such as oxindole and benzofuran derivatives *via* Friedel–Crafts intramolecular Michael addition in high yields. For example, the reaction of diethyl 2-[(*N*-methyl-*N*-phenylcarbamoyl)methylene]malonate (**1a**) in the presence of $ZnCl_2$ at room temperature gave diethyl 2-(1-methyl-2-oxoindolin-3-yl)malonate (**2a**) in 98% yield. The reactions also proceeded with a catalytic amount of a Lewis acid such as $AlCl_3$, $ZnCl_2$, $ZnBr_2$, $Sc(OTf)_3$, or $InBr_3$.

Benzo-annulated heterocyclic compounds such as oxindoles and oxybenzofurans, are important motifs found in biologically active compounds and are useful synthetic intermediates.[1,2] Although various methods for the synthesis of oxindoles are known,[3] they are limited in scope and the development of general methodology for the synthesis of these heterocycles is an important objective. Lewis acids have been demonstrated to promote numerous ring-forming reactions,[4] including: Diels–Alder,[5] [2 + 2] cycloaddition,[6] ene,[7] and alkene–alkene cyclization reactions.[8] On the other hand, known cyclization methods to give benzo-annulated heterocycles using Lewis acids are quite limited,[9] although selective and catalytic Lewis acid-promoted Friedel–Crafts intermolecular Michael additions have been reported.[10] Recently, we reported Lewis acid-promoted intramolecular C–C bond forming reactions of tricarbonyl-substituted enynes.[11] As part of efforts to demonstrate the synthetic potential of highly reactive tricarbonyl-substituted olefins, Lewis acid-promoted intramolecular aromatic cyclizations to afford heterocycles were examined. It was considered that the enhanced reactivity of tricarbonyl-substituted olefins such as ethenetricarboxylate derivative units might lead to highly efficient intramolecular Michael acceptors. Herein, we report a novel cyclization reaction of ethenetricarboxylate derivative aromatic compounds in the presence of various Lewis acids to afford benzo-annulated cyclic products. The reactions also proceeded with a catalytic amount of various Lewis acids which makes the process highly valuable.

Diester-amides **1** were prepared by condensation of the 1,1-diester of 2-hydrogen ethenetricarboxylate (prepared from the 1,1-diester of 2-*tert*-butyl ethenetricarboxylate upon treatment with CF_3CO_2H) with 1-hydroxybenzotriazole (HOBT) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI), followed by reaction with the corresponding *N*-alkyl anilines (eqn 1).[12]



R^1 = Et; R^2 = Me; R^3 = H; 64% (**1a**)
R^1 = CH_2Ph; R^2 = Me; R^3 = H; 40% (**1b**) (1)

† Electronic supplementary information (ESI) available: additional experimental procedures and spectral data and copies of ^1H and ^{13}C NMR spectra for selected compounds. See http://www.rsc.org/suppdata/ob/b4/b408728c/

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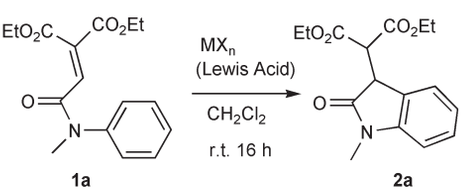
Table 1 Lewis acid-promoted cyclization of **1a**

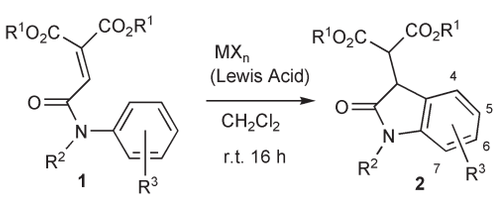
Entry	Lewis acid	Equiv.	**2a**(yield)
1	$ZnCl_2$	1.2	98
2	$ZnBr_2$	1.2	90
3	$ZnCl_2$	0.2	82
4	$ZnBr_2$	0.2	76
5	$AlCl_3$	0.2	79
6	$GaCl_3$	0.2	75
7	$InBr_3$	0.2	91
8	$SnCl_4$	0.2	98
9	$Zn(OTf)_2$	0.2	79
10	$Sc(OTf)_3$	0.2	72

The reaction of diethyl 2-[(*N*-methyl-*N*-phenylcarbamoyl)-methylene]malonate (**1a**) in the presence of $ZnCl_2$ (1.2 equivalents) in CH_2Cl_2 at room temperature for 16 h gave diethyl 2-(1-methyl-2-oxoindolin-3-yl)malonate (**2a**) in 98% yield (eqn 2, Table 1). The reaction also proceeded with catalytic amounts (0.2 equivalents) of Lewis acids such as $AlCl_3$, $ZnCl_2$, $ZnBr_2$, $Sc(OTf)_3$, and $InBr_3$.



(2)

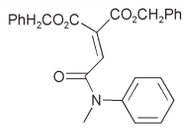
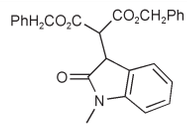
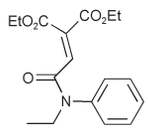
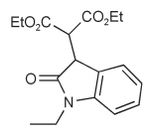
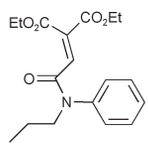
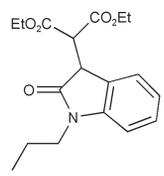
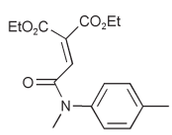
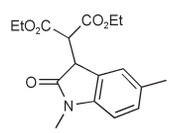
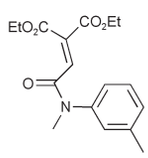
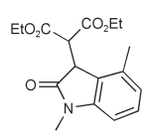
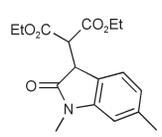
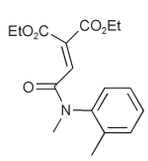
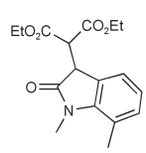
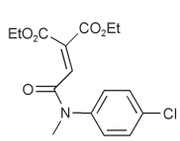
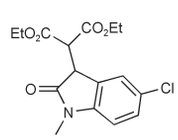
As shown in Table 2, a variety of substrates underwent cyclization to afford oxindoles in high yields. *meta*-Me substituted substrate **1f** gave a 1 : 1 mixture of 4-Me and 6-Me regioisomers, demonstrating that steric hindrance from the methyl group at the 4-position for **2f** does not influence selectivity (entries 8–9). Chloro-substituted substrate **1h** also gave cyclized product **2h** in 86–87% yield (entries 13–14).



(3)

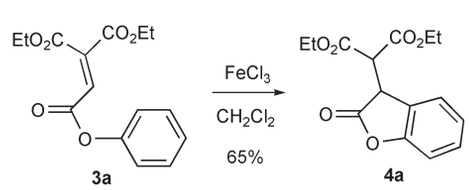
The reaction of triester-substituted substrates was also examined for comparison. The substrates **3** were prepared by

Table 2 Lewis acid-promoted cyclization of **1b**–**g**[a]

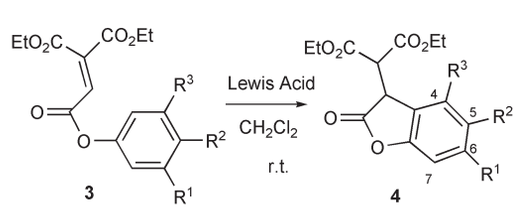
Entry		Substrate	Lewis acid	Equiv.	**2** (yield)	
1	**1b**		$ZnCl_2$	1.2	**2b** (80)	
2	**1b**		$ZnCl_2$	0.2	**2b** (74)[b,c]	
3	**1b**		$Sc(OTf)_3$	0.2	**2b** (67)	
4	**1c**		$ZnBr_2$	1.2	**2c** (76)	
5	**1d**		$ZnBr_2$	1.2	**2d** (72)	
6	**1e**		$ZnCl_2$	1.2	**2e** (98)	
7	**1e**		$ZnBr_2$	1.2	**2e** (65)	
8	**1f**		$ZnCl_2$	1.2	**2f**-4-Me	
					2f-6-Me (79)[d]	
9	**1f**		$ZnBr_2$	1.2	**2f**-4-Me **2f**-6-Me (83)[d]	
10	**1g**		$ZnCl_2$	1.2	**2g** (91)[b]	
11	**1g**		$SnCl_4$	0.2	**2g** (86)	
12	**1g**		$SnCl_4$	1.2	**2g** (90)	
13	**1h**		$SnCl_4$	1.2	**2h** (87)	
14	**1h**		$SnCl_4$	0.2	**2h** (86)	

[a] The reactions were carried out at room temperature for 16 h, unless otherwise noted. [b] Reaction time, 44 h. [c] 6% of **1b** remained. [d] Total yield. Regioisomer ratio 1 : 1.

reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate with the corresponding phenols in the presence of DEAD and PPh_3. The reaction of 1,1-diethyl 2-phenyl ethene-1,1,2-tricarboxylate (**3a**) with $ZnBr_2$ in CH_2Cl_2 at room temperature did not proceed, however, reaction with the stronger Lewis acid $FeCl_3$ (1.2 equiv.) gave diethyl 2-(2,3-dihydro-2-oxobenzofuran-3-yl)-malonate (**4a**) in 65% yield (eqn 4).[13] Various substrates were thus examined to determine the scope of this benzofuran ring formation. Substrates without OMe at the *meta*-position of the phenyl ring did not react with ZnX_2 but only reacted with $FeCl_3$ (eqn 5, Table 3, entries 1–2). On the other hand, the reaction of *m*-methoxyphenyl esters **3d**–**f** with $ZnCl_2$ or $Sc(OTf)_3$ gave benzofuran-2-one derivatives in high yields and regioselectivity (entries 3–9).

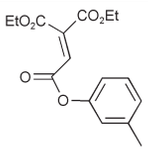
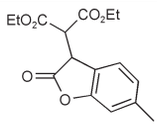
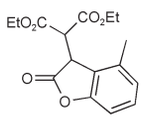
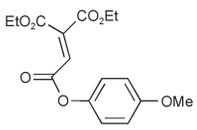
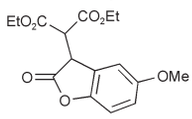
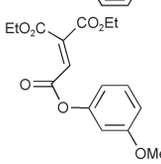
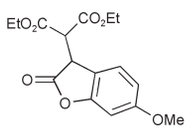
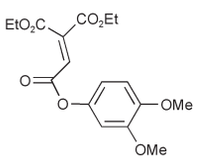
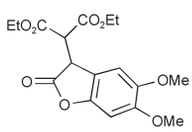
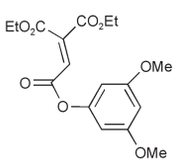
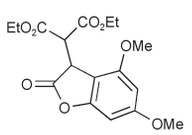


(4)



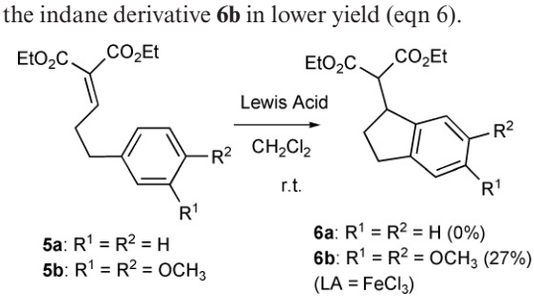
(5)

Table 3 Lewis acid-promoted cyclization of phenyl esters **3b–f**

Entry		Substrate	Lewis Acid	equiv.	**4** (Yield)	
1	**3b**		$FeCl_3$	1.2	**4b**-6-Me	
					4b-4-Me (53)[a]	
2	**3c**		$FeCl_3$	1.2	**4c** (26)	
3	**3d**		$ZnBr_2$	1.2	**4d** (67)[b]	
4	**3d**		$ZnCl_2$	1.2	**4d** (84)[b]	
5	**3d**		$ZnCl_2$	0.2	**4d** (84)[b]	
6	**3e**		$ZnCl_2$	1.2	**4e** (61)[c]	
7	**3e**		$ZnBr_2$	1.2	**4e** (89)[c]	
8	**3e**		$Sc(OTf)_3$	0.2	**4e** (87)[c]	
9	**3e**		$FeCl_3$	1.2	**4e** (92)[c]	
10	**3f**		$ZnCl_2$	1.2	**4f** (88)	
11	**3f**		$ZnCl_2$	0.2	**4f** (64)	
12	**3f**		$ZnBr_2$	1.2	**4f** (91)	
13	**3f**		$FeCl_3$	1.2	**4f** (68)	
14	**3f**		$FeCl_3$	0.2	**4f** (73)	
15	**3f**		$Sc(OTf)_3$	0.2	**4f** (94)	
16	**3f**		$Zn(OTf)_2$	0.2	**4f** (89)	
17	**3f**		$AlCl_3$	0.2	**4f** (82)	

[a] Total yield. The regioisomer ratio for 6-Me and 4-Me is 3 : 1. [b] Almost entirely a single regioisomer (6-OMe) by NMR. A trace amount of a minor product, believed to be the 4-OMe isomer, was present but not characterized. [c] Single regioisomer (5,6-diOMe).

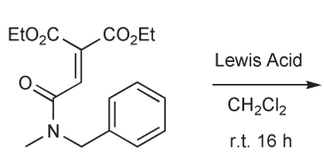
The reaction of diester substrates was also examined. The reaction of diethyl 2-(3-phenylpropylidene)malonate (**5a**) with $ZnBr_2$ or $FeCl_3$ in CH_2Cl_2 at room temperature did not proceed. The substrate with OMe at the *meta*-position of the phenyl ring **5b** did not react with ZnX_2 but reacted with $FeCl_3$ (1.2 equiv.) to give the indane derivative **6b** in lower yield (eqn 6).



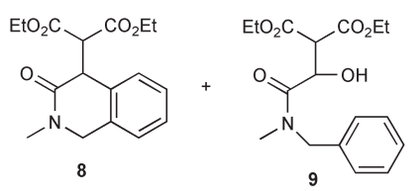
5a: $R^1 = R^2 = H$
5b: $R^1 = R^2 = OCH_3$

6a: $R^1 = R^2 = H$ (0%)
6b: $R^1 = R^2 = OCH_3$ (27%)
(LA = $FeCl_3$) (6)

Six-membered ring formation was examined next. Reaction of benzyl amide **7** with $ZnCl_2$ at room temperature gave only recovered starting material. Reaction with $AlCl_3$, $SnCl_4$, or $FeCl_3$ (1.2 equiv.) at room temperature gave **8** in 26–64% yields along with noncyclized H_2O adduct **9** (eqn 7). In contrast, unsubstituted benzyl ester substrate **10a** did not give cyclized products with $ZnBr_2$, $FeCl_3$ or $AlCl_3$ at room temperature. The substrate with two OMe groups at the *meta*-positions of the phenyl ring, **10b** reacted with $AlCl_3$ (1.2 equiv.) to give cyclized product **11b** in 65% yield (eqn 8).

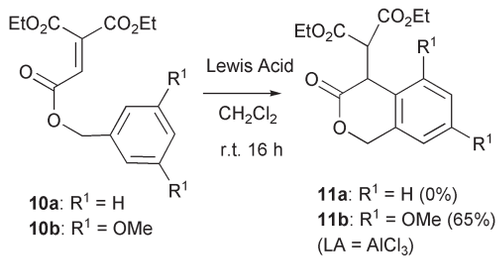


7



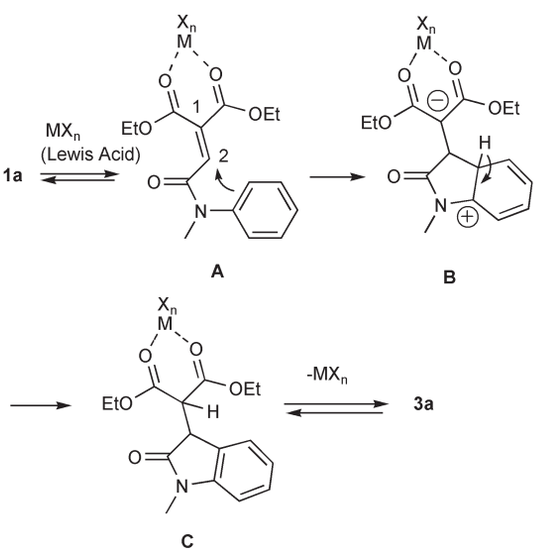
8 **9**

LA = $FeCl_3$; **8** (26%), **9** (63%)
LA = $AlCl_3$; **8** (63%), **9** (13%)
LA = $SnCl_4$; **8** (64%), **9** (12%) (7)



(8)

The probable aromatic substitution mechanism for ring formation exemplified for **3a** is shown in Scheme 1. Nucleophilic attack of the aromatic carbon to the vinyl carbon (C_2) of the electrophilic olefin complexed with Lewis acid in **A** gives a zwitterionic intermediate **B** (σ-complex intermediate for aromatic substitution). Deprotonation at aromatic hydrogen and subsequent protonation of C_1 may lead to intermediate **C**. Dissociation of Lewis acid from the intermediate **C** yields the cyclized product **3**. The nitrogen atom in diester-amide-substituted olefins **1** increases the electron density of the aromatic ring and facilitates the cyclization. For substrate **1f**, the nitrogen atom strongly activates both *ortho*-positions on the ring electronically. Therefore, steric differentiation was not observed compared to substrate **3b** (Table 2 entries 8–9 (regioisomer ratio 1 : 1), Table 3, entry 1 (regioisomer ratio 3 : 1)). Triester substrates need *meta*-methoxy substituents on the aromatic ring in order to react in this catalytic process. For a *meta*-methoxy group compared to a *meta*-methyl group, higher *para*/*ortho* selectivity was observed (Table 2, entries 8–9, Table 3, entries 1 and 3–9, eqn 6). Determination of detailed electronic effects towards regioselectivity are under investigation.



Scheme 1

Six-membered ring formation was not achieved for Lewis acid-promoted HX-incorporative triester or diester/amide enyne cyclization, as studied previously.[11] In this aromatic substitution case, six-membered ring products were obtained, although their formation is a less efficient process compared to five-membered ring formation, mainly because nitrogen or oxygen are not directly connected to aromatic rings. Tricarbonyl structures as Michael acceptors are also effective for this cyclization.

In summary, we have shown a novel and efficient Lewis acid-promoted cyclization reaction yielding benzo-annulated cyclic compounds. The reaction proceeds with mild Lewis acids and in catalytic amounts and the procedure is straightforward. The present reaction should provide an efficient cyclization method for diverse benzo-annulated heterocycles. The highly functionalized cyclized products are suitable for further elaboration to products which are difficult to obtain by known methods. A new utility of tricarbonyl-substituted olefins in organic synthesis has been demonstrated in this study. Further elaboration of the products and development of the use of chiral Lewis acids is under investigation.

Experimental

General methods

Melting points are uncorrected. IR spectra were recorded in the FT-mode. ^{1}H NMR spectra were recorded at 400 MHz. ^{13}C NMR spectra were recorded at 100.6 MHz. ^{1}H chemical shifts are reported in ppm relative to Me_4Si. ^{13}C chemical shifts are reported in ppm relative to $CDCl_3$ (77.1 ppm). ^{13}C mutiplicities were determined by DEPT and HSQC. Mass spectra were recorded at an ionizing voltage of 70 eV by EI or FAB. All reactions were carried out under a nitrogen atmosphere.

Typical cyclization procedure (Table 1, entry 1)

To a solution of **1a** (132 mg, 0.43 mmol) in dichloromethane (0.8 ml) was added $ZnCl_2$ (68 mg, 0.50 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched by water at 0 °C. The mixture was extracted with dichloromethane and the organic phase was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated *in vacuo.* The residue was purified by column chromatography over silica gel eluting with hexane–ether (2 : 1) to give to give **2a** (129 mg, 98%).

Compound 2a. (R_f = 0.4, hexane–ether = 1 : 4) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.988 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 3.24 (s, 3H), 3.92–4.06 (m, 2H), 4.02 (d, J = 3.7 Hz, 1H), 4.22 (d, J = 3.7 Hz, 1H), 4.21–4.34 (m, 2H), 6.83 (d, J = 7.9 Hz, 1H), 7.03 (td, J = 7.6, 1.0 Hz, 1H), 7.29 (tt, J = 7.8, 1.1 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H). Selected NOEs are between δ 3.24 and 6.83, δ 4.02 and 7.40, and δ 4.22 and 7.40; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.73 (q), 14.07 (q), 26.45 (q), 44.65 (d), 52.39 (d), 61.63 (t), 61.93 (t), 107.99 (d), 122.58 (d), 124.96 (d), 125.63 (s), 128.68 (d), 144.76 (s), 166.98 (s), 168.11 (s), 175.36 (s); IR (neat) 2982, 2916, 1719, 1613, 1479, 1323, 1294, 1270, 1093, 1050 cm^{-1}; MS (EI) *m*/*z* 305; exact mass M$^+$ 305.1259 (calcd for $C_{16}H_{19}NO_5$ 305.1263); Anal. calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.62; H, 6.31; N, 4.55%.

Compound 2b. (Table 2) (R_f = 0.2, hexane–ether = 1 : 1) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.93 (s, 3H), 4.02 (d, J = 3.5 Hz, 1H), 4.34 (d, J = 3.5 Hz, 1H), 4.90 (d, J = 12.0 Hz, 1H), 4.92 (d, J = 12.0 Hz, 1H), 5.21 (d, J = 12.2 Hz, 1H), 5.23 (d, J = 12.2 Hz, 1H), 6.65 (d, J = 7.7 Hz, 1H), 6.98 (td, J = 7.6, 1.0 Hz, 1H), 7.05–7.08 (m, 2H), 7.23–7.35 (m, 10H). Selected NOEs are between δ 2.93 and 6.65, δ 4.02 and 7.23–7.35, and δ 4.34 and 7.23–7.35; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 26.16 (q), 44.65 (d), 52.36 (d), 67.60 (t), 67.83 (t), 108.26 (d), 122.61 (d), 124.92 (d), 125.32 (s), 128.43 (d), 128.52 (d), 128.56 (d), 128.59 (d), 128.66 (d), 134.76 (s), 135.08 (s), 144.62 (s), 166.77 (s), 167.92 (s), 175.10 (s); IR (neat) 3066, 3036, 2946, 1715, 1613, 1495, 1470, 1379, 1156 cm^{-1}; MS (EI) *m*/*z* 429; exact mass M$^+$ 429.1573 (calcd for $C_{26}H_{23}NO_5$ 429.1576).

Compound 4a. (eqn 4) (R_f = 0.2, CH_2Cl_2) Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.05 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 4.02–4.10 (m, 2H), 4.22–4.35 (m, 3H), 4.22 (d, J = 3.5 Hz, 1H), 7.11–7.15 (m, 2H), 7.33 (tt, J = 7.7, 1.2 Hz, 1H), 7.42 (d, J = 7.5 Hz, 1H). Selected NOEs are between δ 4.22 and 7.42 and δ 4.22–4.35 and 7.42.; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.70 (q), 14.04 (q), 42.99 (d), 52.78 (d), 62.34 (t), 62.38 (t), 110.76 (d), 124.21 (s), 124.40 (d), 125.32 (d), 129.69 (d), 154.33 (s), 166.31 (s), 167.26 (s), 174.88 (s); IR (neat) 2986, 1808, 1745, 1620, 1481, 1464, 1373, 1340, 1288, 1234, 1180, 1054, 1033 cm^{-1}; MS (EI) *m*/*z* 292; exact mass M$^+$ 292.0938 (calcd for $C_{15}H_{16}O_6$ 292.0947).

Compound 4e. (Table 3) (R_f = 0.2, CH_2Cl_2) Yellow crystals; mp 76–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.08 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 4.02–4.10 (m, 2H), 4.19 (d, J = 3.5 Hz, 1H), 4.24 (dd, J = 3.5, 0.7 Hz, 1H), 4.26–4.34 (m, 2H), 6.73 (s, 1H), 7.03 (d, J = 0.7 Hz, 1H). Selected NOEs are between δ 3.85 and 6.73, δ 3.89 and 7.03, δ 4.19 and 7.03, and δ 4.24 and 7.03; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.73 (q), 14.03 (q), 43.48 (d), 52.91 (d), 56.30 (q), 56.62 (q), 62.20 (t), 62.26 (t), 95.78 (d), 108.70 (d), 114.13 (s), 146.09 (s), 148.36 (s), 150.37 (s), 166.30 (s), 167.50 (s), 175.50 (s); IR (KBr) 2994, 2940, 1794, 1742, 1723, 1630, 1504, 1464, 1317, 1241, 1228, 1160, 1089 cm^{-1}; MS (EI) *m*/*z* 352; exact mass M^+ 352.1161 (calcd for $C_{17}H_{20}O_8$ 352.1158).

Compound 4f. (Table 3) (R_f = 0.4, CH_2Cl_2) Pale yellow crystals; mp 96–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.13 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 3.799 (s, 3H), 3.803 (s, 3H), 3.98–4.08 (m, 1H), 4.11–4.19 (m, 1H), 4.30–4.35 (m, 2H), 4.35 (d, J = 4.0 Hz, 1H), 4.41 (d, J = 4.0 Hz, 1H), 6.19 (d, J = 2.0 Hz, 1H), 6.33 (d, J = 2.0 Hz, 1H). Selected NOEs are between δ 4.41 and 3.799 or 3.803, δ 6.19 and 3.799, 3.803, and δ 6.33 and 3.799 or 3.803.; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.84 (q), 14.08 (q), 41.99 (d), 51.33 (d), 55.72 (q), 55.83 (q), 61.84 (t), 62.37 (t), 89.69 (d), 94.28 (d), 103.30 (s), 155.69 (s), 156.53 (s), 162.32 (s), 166.63 (s), 167.10 (s), 174.69 (s); IR (KBr) 2988, 1812, 1740, 1729, 1632, 1613, 1510, 1468, 1348, 1156, 1048 cm^{-1}; MS (EI) *m*/*z* 352; exact mass M^+ 352.1154 (calcd for $C_{17}H_{20}O_8$ 352.1158); Anal. calcd for $C_{17}H_{20}O_8$: C, 57.95; H, 5.72. Found: C, 57.70; H, 5.71%.

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References and notes

1 (*a*) G. A. Cordell, *Introduction to Alkaloids—A Biogenetic Approach*, Wiley-Interscience, New York, 1981; (*b*) J. S. Bindra, Oxindole Alkaloids in *The Alkaloids—Chemistry and Physiology*, ed. R. H. F. Manske, Academic Press, New York, 1973, vol. XIV, pp. 83–121; (*c*) G. Cravotto, G. B. Giovenzana, T. Pilati, M. Sisti and G. Palmisano, *J. Org. Chem.*, 2001, **66**, 8447.

2 (*a*) D. E. Fuerst, B. M. Stoltz and J. L. Wood, *Org. Lett.*, 2000, **2**, 3521; (*b*) E. Vedejs and J. Wang, *Org. Lett.*, 2000, **2**, 1031.

3 (*a*) R. R. Goehring, Y. P. Sachdeva, J. S. Pisipati, M. C. Sleevi and J. F. Wolfe, *J. Am. Chem. Soc.*, 1985, **107**, 435; (*b*) E. J. Hennessy and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 12084; (*c*) K. H. Shaughnessy, B. C. Hamann and J. F. Hartwig, *J. Org. Chem.*, 1998, **63**, 6546; (*d*) S. Lee and J. F. Hartwig, *J. Org. Chem.*, 2001, **66**, 3402.

4 (*a*) *Lewis Acids in Organic Synthesis*, ed. H. Yamamoto, Wiley-VCH, Weinheim, 2000, vol. 1–2; (*b*) *Lewis Acid Reagents*, ed. H. Yamamoto, Oxford University Press, New York, 1999.

5 (*a*) W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 876; (*b*) S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1; (*c*) D. M. Birney and K. N. Houk, *J. Am. Chem. Soc.*, 1990, **112**, 4127; (*d*) W. Carruthers, in *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, Oxford, 1991, pp. 140–208.

6 (*a*) T. Takeda, T. Fujii, K. Morita and T. Fujiwara, *Chem. Lett.*, 1986, 1311; (*b*) K. Narasaka, Y. Hayashi, H. Shimadzu and S. Niihata, *J. Am. Chem. Soc.*, 1992, **114**, 8869; (*c*) W. Srisiri, A. B. Padias and H. K. Hall, Jr., *J. Org. Chem.*, 1994, **59**, 5424; (*d*) R. D. Clark and K. G. Untch, *J. Org. Chem.*, 1979, **44**, 248, 253; (*e*) M. R. Baar, P. Ballesteros and B. W. Roberts, *Tetrahedron Lett.*, 1986, **27**, 2083; (*f*) T. Okauchi, T. Kakiuchi, N. Kitamura, T. Utsunomiya, J. Ichikawa and T. Minami, *J. Org. Chem.*, 1997, **62**, 8419.

7 (*a*) B. B. Snider, *Acc. Chem. Res.*, 1980, **13**, 426; (*b*) K. Narasaka, Y. Hayashi and S. Shimada, *Chem. Lett.*, 1988, 1609; (*c*) L. F. Tietze, U. Beifuss, M. Ruther, A. Rühlmann, J. Antel and G. M. Sheldrick, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1186; (*d*) L. F. Tietze and U. Beifuß, *Synthesis*, 1988, 359; (*e*) T. Minami, T. Utsunomiya, S. Nakamura, M. Okubo, N. Kitamura, Y. Okada and J. Ichikawa, *J. Org. Chem.*, 1994, **59**, 6717.

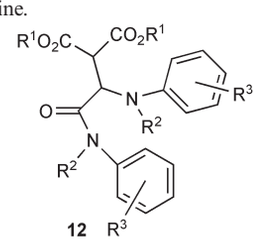
8 (*a*) B. B. Snider and D. M. Roush, *J. Org. Chem.*, 1979, **44**, 4229; (*b*) L. F. Tietze and M. Ruther, *Chem. Ber.*, 1990, **123**, 1387; (*c*) L. F. Tietze and C. Schünke, *Eur. J. Org. Chem.*, 1998, 2089.

9 (*a*) M. Agnusdei, M. Bandini, A. Melloni and A. Umani-Ronchi, *J. Org. Chem.*, 2003, **68**, 7126; (*b*) A. H. Beckett, R. W. Daisley and J. Walker, *Tetrahedron*, 1968, **24**, 6093.

10 (*a*) W. Zhuang, T. Hansen and K. A. Jørgensen, *Chem. Commun.*, 2001, 347; (*b*) J. Zhou and Y. Tang, *J. Am. Chem. Soc.*, 2002, **124**, 9030; (*c*) N. Gathergood, W. Zhuang and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2000, **122**, 12517; (*d*) K. B. Jensen, J. Thorhauge, R. G. Hazell and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2001, **40**, 160; (*e*) A. Ishii, V. A. Soloshonok and K. Mikami, *J. Org. Chem.*, 2000, **65**, 1597, and references therein; (*f*) Y. Yuan, X. Wang, X. Li and K. Ding, *J. Org. Chem.*, 2004, **69**, 146.

11 (*a*) S. Yamazaki, K. Yamada, S. Yamabe and K. Yamamoto, *J. Org. Chem.*, 2002, **67**, 2889; (*b*) S. Yamazaki, K. Yamada and K. Yamamoto, *Org. Biomol. Chem.*, 2004, **2**, 257.

12 The optimized reaction conditions are as follows. The 1,1-diester of 2-hydrogen ethenetricarboxylate was reacted with 1-hydroxybenzotriazole (HOBT) in the presence of EDCI for 1 h at 0 °C, then the corresponding *N*-alkyl aniline was added and the resulting mixture stirred at room temperature overnight. When all the reagents were mixed at once (see Electronic supplementary information†), considerable amounts of byproducts **12** were produced and the yields of **1** decreased. Probably Michael addition of the corresponding *N*-alkyl anilines to 1,1-diester of 2-hydrogen ethenetricarboxylate occurred before condensation of the carboxyl group and the aniline.



12 R^3

The reaction with *N*-unsubstituted aniline under the conditions gave diester amide **1** only in very low yield.

13 The yield (65%) contains small amounts of unidentified byproducts which could not be removed by column chromatography. Pure **4a** was isolated in 36% yield.