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Notes

Asymmetric Synthesis of 1,1-Diarylalkanes *via* Friedel–Crafts Alkylation of Donor–Acceptor Cyclopropanes with Electron-Rich Benzene

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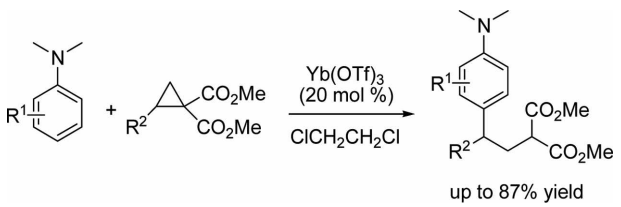
Donor acceptor (D A) cyclopropanes have recently been recognized as one of the powerful building blocks in organic synthesis owing to their accessibility and broad scope of reactivity for generating a diverse array of products.[1] Due to the synergistic push–pull character imparted to the ring by the donor and acceptor functionalities, D–A cyclopropanes have been employed in numerous synthetic methodologies to furnish various acyclic and cyclic compounds using cycloaddition, ring–opening, and rearrangement reactions. Various cycloadditions of D–A cyclopropanes with dienes, dipolarophiles, or 1,3-dipoles, such as [3 + 2], [3 + 3], [4 + 3]-annulation, afford highly functionalized five, six, or seven-membered carbocycles and heterocycles.[2] Ring-opening reaction, which give access to 1,3-bifunctionalized compounds, are the most common transformations of D–A cyclopropanes.[3] Among the ring-opening reactions, Friedel Crafts alkylation is a powerful tool for the addition of carbon nucleophiles to D A cyclopropanes.

Recently, we developed a Friedel–Crafts type ring-opening reaction of D–A cyclopropanes with electron-enriched benzenes, including *N,N*-dialkylaniline, providing a valuable method for the synthesis of 1,1-diarylalkane derivatives (*Scheme* 1).[4] *N,N*-Dialkylaniline acts as a good nucleophile, ans was not deactivated or decomposed by Lewis acids such as $Yb(OTf)_3$, which was used as a catalyst in this Friedel–Crafts reaction.

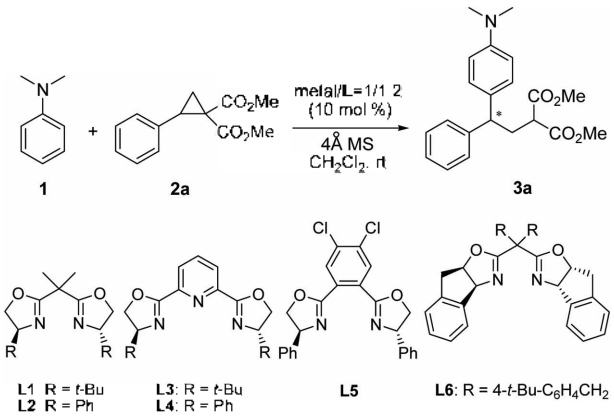


***Scheme* 1.** Lewis acid-catalyzed Friedel-Crafts alkylation of D-A cyclopropanes with electron-rich benzenes.

1,1-Diarylalkanes are active against autoimmune disorders, cancer, inflammation, insomnia, and osteoporosis.[5] This scaffold is found in numerous biologically active natural products and notable pharmaceuticals, including (–)-cyclogalgravin, (+)-sertraline detrol, peperomin B, and ormeloxifene. Despite their potent biological activities and unique structural features, the various asymmetric syntheses of enantioenriched 1,1-diarylalkanes have not been reported until now owing to their structural features.[6] The control of stereochemistry in 1,1-diarylalkanes remains challenging, and substantial effort has been put into the development of an enantioselective synthesis method. Herein, we report the synthesis of enantioenriched 1,1-diarylalkanes using the magnesium-catalyzed asymmetric Friedel–Crafts alkylation of D–A cyclopropanes with electron-enriched benzenes.

Initially, the asymmetric Friedel Crafts alkylation of *N,N*-dimethylaniline (**1**) with dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**2a**) in the presence of $Cu(OTf)_2$ and bis(oxazoline) ligands[7] was selected as the model reaction (*Table* 1). The reaction of **1** (1.0 equiv) with **2a** (1.2 equiv) was carried out in the presence of $Cu(OTf)_2$ (0.1 equiv), *t*-Bu-box **L1** (0.12 equiv), and 4 Å molecular sieves in CH_2Cl_2 at room temperature. However, this reaction did not afford the desired product **3a** (entry 1). When the same reaction was performed with MgI_2/**L1** as the catalyst, product **3a** was produced, albeit with low isolated yield and enantioselectivity (15% yield, 56:44 er, entry 2). Encouraged by this result, other bis(oxazoline)-MgI_2 catalysts were investigated under similar reaction conditions. The yield was higher using Ph-box **L2** as a ligand (39% yield, entry 3). Significantly improved reaction efficiency was observed with the ligand *t*-Bu-pybox **L3**, which gave the desired product **3a** in high yield with slightly increased enantioselectivity (75% yield, 59:41 er, entry 4). Improved enantioselectiv-

***Table* 1.** Ligand screening and reaction optimization[a]



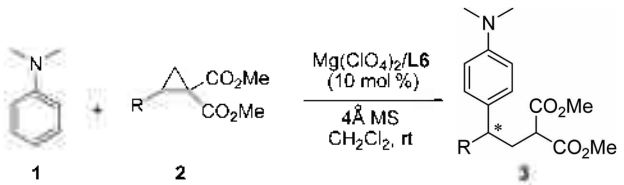
Entry	Metal precursor	Ligand	Time (h)	Yield (%)[b]	er[c]
1	$Cu(OTf)_2$	**L1**	48	–[d]	nd
2	MgI_2	**L1**	48	15	56:44
3	MgI_2	**L2**	48	39	54:46
4	MgI_2	**L3**	48	75	59:41
5	MgI_2	**L4**	48	27	77:23
6	$Yb(OTf)_3$	**L3**	70	71	58:42
7	$Yb(OTf)_3$	**L4**	70	47	54:46
8	$Mg(OTf)_2$	**L3**	70	39	69:31
9	$Mg(OTf)_2$	**L4**	70	29	66:34
10	MgI_2	**L5**	70	28	69:31
11	MgI_2	**L6**	70	30	82:18
12	$Mg(ClO_4)_2$	**L6**	70	34	84:16

[a]All of the reactions were carried out in CH_2Cl_2 (0.1 M) with **1** (0.10 mmol), **2a** (0.12 mmol), 4 Å molecular sieve (20 mg), metal precursor (10 mol %), and L (12 mol %).
[b]Isolated yield after chromatographic purification.
[c]Determined by chiral-phase HPLC analysis.
[d]No desired product obtained.

ity was observed using ligand Ph-pybox **L4**, despite a low isolated yield (77:23 er, entry 5). Other metal catalyst systems, such as $Yb(OTf)_3$ and $Mg(OTf)_2$ with **L3** and **L4**, gave inferior results compared with the MgI_2 catalysts (entries 6–9). Upon further surveying the bidentate box ligands, it was revealed that 1,2-bis(oxazolinebenzene) ligand **L5**-MgI_2 catalyst afforded product **3a** in low yield with moderate enantioselectivity (entry 10). However, a box ligand containing two aryl side-arm groups improved the enantioselectivity in this reaction. An indane-box ligand **L6**-MgI_2 catalyst gave the desired product **3a** in 30% yield with high enantioselectivity (82:18 er, entry 11), but starting material **2a** was still slowly decomposed in this reaction condition. Replacing MgI_2 with $Mg(ClO_4)_2$ led to a slight increase in yield and enantioselectivity (34% yield, 84:16 er, entry 12).

With the optimized reaction conditions in hand (1 equiv

***Table* 2.** Variation of the donor-acceptor cyclopropanes[a]



Entry	R	Time (h)	**3**	Yield (%)[b]	er[c]
1	Ph	70	**3a**	34	84:16
2[d]	*p*-$MeOC_6H_4$	76	**3b**	55	78:22
3	3,4-$(MeO)_2C_6H_3$	74	**3c**	68	85:15
4	*p*-MeC_6H_4	70	**3d**	59	71:29
5	*p*-FC_6H_4	70	**3e**	27	80:20
6	2-furanyl	70	**3f**	26	68:32
7	2-thienyl	94	**3g**	58	53:47

[a]All of the reactions were carried out in CH_2Cl_2 (0.1 M) with **1** (0.10 mmol), **2** (0.12 mmol), 4 Å molecular sieve (20 mg), metal precursor (10 mol %), and **L6** (12 mol %).
[b]Isolated yield after chromatographic purification.
[c]Determined by chiral-phase HPLC analysis.
[d]Stirred in toluene.

of **1**, 1.2 equiv of **2**, 4 Å molecular sieve, 10 mol % of $Mg(ClO_4)_2$, **L6**, and 0.1 M solution of CH_2Cl_2 at rt), the reaction scope of the D–A cyclopropanes was examined (*Table* 2). Firstly, D–A-substituted cyclopropane substrates with electron-rich donor moieties seemingly exhibited higher reactivities than those with unsubstituted-phenyl ring or electron-withdrawing moieties, producing corresponding the 1,1-diaryl products **3** in good yields (entries 2–3 vs 1 and 5). Notably, D–A-substituted cyclopropanes with 3,4-dimethoxy-substituted aryl groups furnished highest yield and enantioselectivity (68% yield, 85:15 er, entry 12). The reaction was also extended to substrates with heteroaryl groups, but the low enantioselectivities were obtained (entries 6–7).

In summary, we have described a magnesium-catalyzed enantioselective Friedel–Crafts alkylation of D–A cyclopropanes with electron-enriched benzenes. This asymmetric reaction was performed with various metal precursors and bidentate bis(oxazoline) ligands, of which the indane-box ligand **L6**-$Mg(ClO_4)_2$ system was the best catalyst. The reaction of *N*,*N*-dimethylaniline (**1**) with various D–A cyclopropanes afforded enantioenriched 1,1-diarylalkanes (up to 85:15 er). Current work is focused on expanding the scope of this asymmetric catalytic reaction to other substrates.

EXPERIMENTAL

General procedure for indane-bis(oxazoline)/$Mg(ClO_4)_2$-catalyzed asymmetric Friedel–Crafts alkylation reac-

tion: To a flame-dried flask charged with $Mg(ClO_4)_2$ (0.010 mmol, 0.10 equiv), indane-bis(oxazoline) **L6** (0.012 mmol, 0.12 equiv), and 4 Å molecular sieve (20 mg, 3.0% w/v) in an inert atmosphere, was added CH_2Cl_2 (0.75 mL) and the resulting mixture was stirred vigorously for q h under an inert atmosphere. A solution of *N*,*N*-methylaniline **1** (0.10 mmol, 1.0 equiv) and cyclopropane (0.12 mmol, 1.2 equiv) in CH_2Cl_2 (0.25 mL) was then added *via* syringe. The resulting mixture was stirred at rt until complete consumption of *N*,*N*-methylaniline **1** was observed as determined by TLC. The resulting mixture was directly purified on silica gel column chromatography using ethyl acetate and hexane as eluents to afford the desired 1,1-diarylalkane compound **3**.

Dimethyl 2-(2-(4-(dimethylamino)phenyl)-2-phenylethyl)malonate (3a). colorless gum; $[\alpha]_D^{23}$ = −74.5 (*c* = 0.066, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.20 (m, 4H), 7.16 (t, *J*=7.0 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J*=8.6 Hz, 2H), 3.84 (t, *J*=8.0 Hz, 1H), 3.70 (d, *J*=2.0 Hz, 6H), 3.30 (t, *J*=7.4 Hz, 1H), 2.90 (s, 6H), 2.62 (t, *J*=7.7 Hz, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ 169.93, 169.90, 149.33, 144.26, 131.12, 128.52, 127.79, 126.30, 112.83, 52.54, 52.53, 50.12, 47.73, 40.68, 34.72; IR (film) 2951, 2708, 1751, 1613, 1513, 1434, 1310, 1223, 1148, 1047 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{21}H_{25}NO_4$: 355.1784 Found: 355.1782: 84:16 er; Chiralpak IA column and IA guard column (5% EtOH:hexanes, 1.0 mL/min flow, λ = 254 nm); *minor*-isomer t_r = 8.4 min and *major*-isomer t_r = 9.4 min.

Dimethyl 2-(2-(4-(dimethylamino)phenyl)-2-(4-methoxyphenyl)ethyl)-malonate (3b). colorless gum; $[\alpha]_D^{29}$ = 6.7 (*c* = 0.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 8.7 Hz, 2H), 3.79 (t, *J* = 8.0 Hz, 1H), 3.76 (s, 3H), 3.70 (d, *J* = 1.3 Hz, 6H), 3.29 (t, *J* = 7.4 Hz, 1H), 2.90 (s, 6H), 2.59 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.95, 158.02, 149.29, 136.38, 131.58, 128.74, 128.41, 113.89, 112.85, 55.25, 52.52, 50.14, 46.88, 40.71, 34.93; IR (film) 2951, 1732, 1610, 1509, 1435, 1341, 1246, 1225, 1153, 1034 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{22}H_{27}NO_5$: 385.1889 Found: 385.1867; 78:22 er; Chiralpak IA column and IA guard column (5% EtOH: hexanes, 1.0 mL/min flow, λ = 254 nm); *minor*-isomer t_r = 11.4 min and *major*-isomer t_r = 13.3 min.

Dimethyl 2-(2-(4-(dimethylamino)phenyl)-2-(3,4-dimethoxyphenyl)-ethyl)malonate (3c). colorless gum; $[\alpha]_D^{29}$ = −7.8 (*c* = 0.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.6 Hz, 2H), 6.78 (s, 2H), 6.72 (s, 1H), 6.67 (d, *J* = 8.7 Hz, 2H), 3.83 (s, 6H), 3.79 (t, *J* = 8.1 Hz, 1H), 3.70 (d, *J* = 0.7 Hz, 6H), 3.31 (t, *J* = 7.3 Hz, 1H), 2.90 (s, 6H), 2.59 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.95, 149.32, 148.88, 147.47, 136.82, 131.39, 128.36, 119.59, 112.84, 111.25, 111.15, 55.88, 55.84, 52.52, 50.11, 47.32, 40.69, 34.93; IR (film) 2951, 2836, 1731, 1612, 1514, 1437, 1342, 1234, 1142, 1028 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{23}H_{29}NO_6$: 415.1995 Found: 415.1992; 85:15 er; Chiralpak IA column and IA guard column (5% *i*-PrOH:hexanes, 1.0 mL/min flow, λ = 254 nm); *major*-isomer t_r = 26.6 min and *minor*-isomer t_r = 29.2 min.

Dimethyl 2-(2-(4-(dimethylamino)phenyl)-2-*p*-tolylethyl)malonate (3d). colorless gum; $[\alpha]_D^{29}$ = 8.6 (*c* = 0.41, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 13.4, 7.6 Hz, 6H), 6.66 (d, *J* = 8.7 Hz, 2H), 3.80 (t, *J* = 8.1 Hz, 1H), 3.69 (d, *J* = 1.6 Hz, 6H), 3.30 (t, *J* = 7.4 Hz, 1H), 2.89 (s, 6H), 2.60 (t, *J* = 7.7 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.04, 149.41, 141.33, 135.86, 131.57, 129.31, 128.55, 127.76, 112.98, 52.61, 50.25, 47.41, 40.81, 34.89, 21.09; IR (film) 2950, 1732, 1612, 1519, 1434, 1342, 1273, 1224, 1152 cm^{-1}; HRMS (EI) m/z calcd for $[M]^-$ $C_{22}H_{27}NO_4$: 369.1940 Found: 369.1954; 71:29 er; Chiralpak IA column and IA guard column (2% EtOH: hexanes, 1.0 mL/min flow, λ = 254 nm); *minor*-isomer t_r = 10.4 min and *major*-isomer t_r = 13.6 min.

Dimethyl 2-(2-(4-(dimethylamino)phenyl)-2-(4-fluorophenyl)ethyl)-malonate (3e). colorless gum; $[\alpha]_D^{29}$ = 3.3 (*c* = 0.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.95 (t, *J* = 8.7 Hz, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 3.83 (t, *J* = 8.1 Hz, 1H), 3.70 (d, *J* = 4.4 Hz, 6H), 3.28 (t, *J* = 7.4 Hz, 1H), 2.90 (s, 6H), 2.59 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.91, 169.90, 162.70, 160.27, 149.49, 140.18, 140.15, 130.84, 129.32, 129.24, 128.52, 115.45, 115.24, 112.91, 52.66, 52.64, 50.14, 47.08, 40.72, 34.94; IR (film) 2952, 1732, 1613, 1520, 1507, 1434, 1344, 1275, 1220, 1157 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{21}H_{24}FNO_4$: 373.1689 Found: 373.1674; 80:20 er; Chiralpak IA column and IA guard column (2% *i*-PrOH:hexanes, 1.0 mL/min flow, λ = 254 nm); *minor*-isomer t_r = 17.5 min and *major*-isomer t_r = 18.7 min.

Dimethyl 2-(2-(4-(dimethylamino)phenyl)-2-(furan-2-yl)ethyl)malonate (3f). colorless gum; $[\alpha]_D^{29}$ = −25.6 (*c* = 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 0.9 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.68 (d, *J* = 8.7 Hz, 2H), 6.27 (dd, *J* = 2.9, 1.9 Hz, 1H), 6.06 (d, *J* = 3.1 Hz, 1H), 3.93–3.84 (m, 1H), 3.71 (d, *J* = 22.5 Hz, 6H), 3.31 (dd, *J* = 8.0, 6.8 Hz, 1H), 2.91 (s, 6H), 2.67 (dt, *J* = 15.2, 7.6 Hz, 1H), 2.45 (ddd, *J* = 13.9, 8.9, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.85, 169.82, 157.25, 149.80, 141.63, 128.75, 128.64, 112.92, 110.10, 105.62, 52.69, 52.66,

49.85, 42.10, 40.76, 33.86; IR (film) 2952, 1732, 1613, 1520, 1435, 1345, 1222, 1153 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{19}H_{23}NO_5$: 345.1576 Found: 345.1543; 68:32 er; Chiralpak IA column and IA guard column (2% EtOH: hexanes, 1.0 mL/min flow, λ = 254 nm); *major*-isomer t_r = 11.4 min and *mino* -isomer t_r = 13.1 min.

Dimethyl 2-(2-(4-(dimethylamino)phenyl)-2-(thiophen-2-yl)ethyl)malonate (3g). colorless gum; $[\alpha]_D^{29}$ = 2.8 (*c* = 0.31, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 8.5, 4.8 Hz, 3H), 6.90 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.84 (d, *J* = 3.4 Hz, 1H), 6.68 (d, *J* = 8.7 Hz, 2H), 4.12–4.04 (m, 1H), 3.70 (d, *J* = 19.0 Hz, 6H), 3.33 (dd, *J* = 8.1, 6.7 Hz, 1H), 2.91 (s, 6H), 2.70 (ddd, *J* = 15.2, 8.1, 7.1 Hz, 1H), 2.58 (ddd, *J* = 13.8, 9.1, 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.75, 169.72, 149.65, 148.92, 130.55, 128.40, 126.59, 123.85, 123.80, 112.75, 52.58, 49.94, 43.47, 40.62, 36.19; IR (film) 2951, 1732, 1612, 1520, 1434, 1346, 1221, 1155 cm^{-1}; HRMS (EI) m/z calcd for $[M]^+$ $C_{19}H_{23}O_4S$: 361.1348 Found: 361.1313; 53:47 er; Chiralpak IA column and IA guard column (2% EtOH:hexanes, 1.0 mL/min flow, λ = 254 nm); *major*-isomer t_r = 12.8 min and *mino* -isomer t_r = 15.5 min.

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