Stereoselective Conjugate Addition Reactions of α,β-Unsaturated *tert*-Butyl Esters with Aryllithium Reagents†

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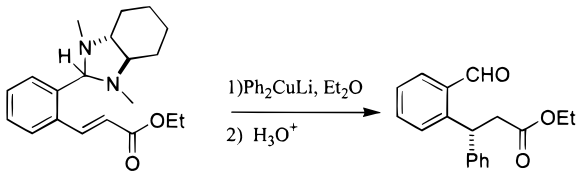
Chiral β,β-diaryl propionic acid derivatives and related compounds have significant and diverse biological activity. This structural element is present in compounds which have reported activities as antiarrhythmics,[1,2] vasodilators (Ca-modulin antagonists),[1,3] antidepressives,[1,4,5] antihistamines,[1] and controllers of cerebral insufficiency.[6] As such, synthetic methods are required for the preparation of a wide variety of compounds of this general structure,[1,2,4,6−10] especially in an optically pure form.[5,7−9] In this regard we were attracted to methodology developed by Alexakis involving stereoselective 1,4-addition of lithium diphenyl cuprate to α,β-unsaturated ethyl ester **1** possessing a neighboring chiral controller



1 **2**

(chiral imidazolidine).[8]

This chemistry features high stereoselectivity, facile attachment and removal of the chiral auxiliary, and the aldehyde function in the product **2** provides a handle for further functionalization. However, for our purposes, it was found that the use of Gilman-type cuprates for this transformation was not always practical. In particular, the requirement of 2 equiv of cuprate for full conversion results in the waste of 3 equiv of transferable ligand.[11] Also, in our hands, more hindered aryl cuprates (e.g., ortho-substituted aryl cuprates) were either difficult to form or did not react cleanly.[12] Although aryllithium reagents are easily prepared and are highly reactive, their use in this reaction has not been reported, presumably due to competing 1,2-addition with α,β-unsaturated ethyl esters.[13] It was proposed that use of the corresponding *tert*-butyl esters would minimize the 1,2 mode of addition.[14] Therefore, we decided to investigate the reactions of aryllithium reagents with α,β-unsaturated *tert*-butyl esters (e.g., **3b/3c**) possessing chiral imidazolidine (**3b**) or oxazolidine (**3c**) auxiliaries in order to develop a general method for enantioselective synthesis of chiral β,β-diarylpropanoates **4** (Scheme 1). The chiral imidazolidine and oxazolidines **3b/3c** were selected for initial studies since they are prepared from aldehyde **3a**[15] and the readily available and inexpensive starting materials (1*R*,2*R*)-bis-*N*-methylamino cyclohexane and (1*S*,2*S*)-pseudoephedrine, respectively.

Our studies began with a comparison of the reactions of Ph_2CuLi and PhLi with unsaturated ester **3b** using Et_2O as the solvent (Table 1, entries 1 and 3). As expected, the reaction involving PhLi (2 equiv)[16] was complete within 1 h at −78 °C, while the reaction involving Ph_2CuLi (2 equiv) required warming to 0 °C. After workup (aqueous NH_4Cl), the auxiliaries were removed (THF−aqueous HOAc, 25 °C), and the products were purified by silica gel chromatography. The enantiomeric excesses were determined using chiral supercritical fluid chromatography (SFC) on the purified products. It was found that PhLi and Ph_2CuLi reacted with **3b** in Et_2O to give the 1,4-addition product **5** (<5%

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(8) Diastereoselective conjugate addition of R_2CuLi to cinnamates bearing a chiral imidazolidine or an oxazolidine auxiliary: Alexakis, A.; Sedrani, R.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 4411.

(9) (a) Christenson, B.; Hallnemo, G.; Ullenius, C. *Tetrahedron* **1991**, *47*, 4739. Stereoselective conjugate addition using chiral cuprates: (b) Malmberg, H.; Nilsson, M.; Ullenius, C. *Tetrahedron Lett.* **1982**, *23*, 3823. (c) Andersson, S.; Jagner, S.; Nilsson, M.; Urso, F. *J. Organomet. Chem.* **1986**, *301*, 257−267.

(10) Nosseir, M. H.; Aziz, G.; Doss, N. L.; Rish, A. S. *Indian J. Chem.* **1974**, *12*, 668−670.

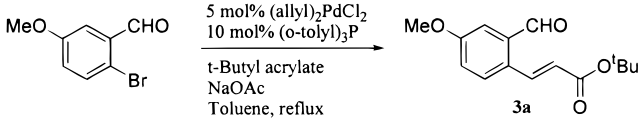
(11) This problem may be avoided by use of a mixed cuprate with a nontransferable ligand. See footnote 9 and also Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945−948.

(12) For example, the cuprate prepared from 4-bromo-3-methyl anisole did not react cleanly with **1**, providing mainly the 1,2-1,4-over addition product.

(13) Reaction of *p*-methoxyphenyllithium with **1** provided mainly the products of 1,2-addition (including the 1,2-addition product, and the 1,2-1,4 and 1,2-1,2-over addition products). For a review of organolithium chemistry, see: Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon Press: New York, 1974.

(14) Conjugate addition reactions of unsaturated *sec*- and *tert*-butyl esters: (a) Cooke, M. P., Jr. *J. Org. Chem.* **1984**, *49*, 1144−1146. (b) Munch-Petersen, J. *J. Org. Chem.*, **1957**, *22*, 170−176. (c) Unsaturated esters of 2,6-di-*tert*-butyl-4-methoxyphenol undergo conjugate addition reactions with organolithium reagents: Cooke, M. P. *J. Org. Chem.* **1986**, *51*, 1637−1638. (d) Conjugate addition reactions of trityl enones with organolithium derivatives: Seebach, D.; Ertas, M.; Locher, R.; Schweizer, W. B. *Helv. Chim. Acta* **1985**, *68*, 264−282. (e) 1,4-addition of organolithiums in charge-directed systems: Cooke, M. P., Jr.; Pollock, C. M. *J. Org. Chem.* **1993**, *58*, 474−7481.

(15) **3a** was prepared from 2-bromo-5-methoxybenzaldehyde via Heck reaction: see Experimental Section.



3a

(16) Reactions were carried out with 2 equiv of ArLi to guarantee complete reaction. When 1 equiv of ArLi was used, the ee of the final product was similar to that obtained using 2 equiv of ArLi, but the reactions did not proceed to completion.

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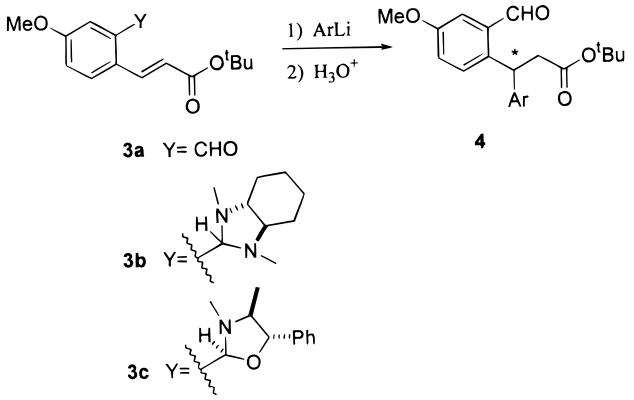
Scheme 1

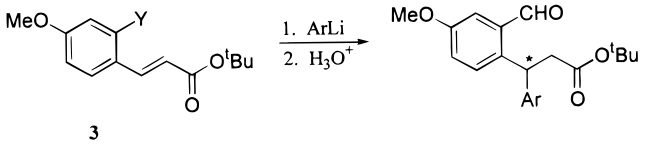


1,2-addition products were observed)[17] with similar stereoselectivity and with the same absolute stereochemistry (assigned the *R* configuration in accordance with the work of Alexakis).[8,18] Further examination of the 1,4-addition reactions involving PhLi indicated that improved enantioselectivity could be obtained by use of the imidazolidine **3b** in THF (entry 2) or by use of the (1*S*,2*S*)-pseudoephedrine-based oxazolidine **3c** in Et_2O (entry 4).

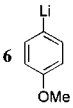
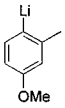
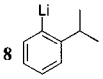
At this point the conclusion was made that the use of copper-based reagents for this transformation is not essential, and that high stereoselectivity might generally be attainable using aryllithium reagents. Thus, we investigated the reactions of substituted aryllithium reagents **6**−**10** with **3b/3c** using both THF and Et_2O as the solvent (Table 1, entries 6−25). Several points should be made regarding these data. First, the reactions proceeded efficiently in most cases to give good yields of the 1,4-adducts **11**−**15**, with little (<5%) 1,2-addition being observed. The ^{1}H NMR spectra of compounds **5** and **11**−**15** (Eu(hfc)$_3$, C_6D_6) consistently showed upfield shifts for the major enantiomer (early eluting relative to minor enantiomer by SFC), implying that these products have the same absolute configuration (assigned as *R*). Enantioselectivities were highly dependent on the structure of the nucleophile and chiral auxiliary, as well as on the solvent. In general, the enantioselectivities were higher in THF than in Et_2O for reactions involving the (1*R*,2*R*)-bis-*N*-methylamino cyclohexane-based imidazolidine **3b** (entries 6 vs 7, 10 vs 11, 14 vs 15, 22 vs 23). Conversely, the enantioselectivities were generally higher in Et_2O than in THF for reactions involving the (1*S*,2*S*)-pseudoephedrine-based oxazolidine **3c** (entries 8 vs 9, 12 vs 13, 24 vs 25). However, for a given aryllithium reagent, it was not possible to predict which chiral auxiliary and solvent combination would give the best enantioselectivity. In each case, the enantioselectivity (as high as 97% ee) was maximized experimentally by appropriate matching of the solvent and auxiliary.

Next, the effect of structural variation of the oxazolidine auxiliary was investigated. For this study the chiral

Table 1. Reactions[a] of Aryl Organometallic Reagents with 3b/3c



3

Entry	3	ArM[b]	Solvent	Yield (%)[c]	ee (%)[d]	Product
1	**3b**	PhLi	Et_2O	62	48	**5**
2			THF	86	66	
3		Ph_2CuLi	Et_2O	79	59	
4	**3c**	PhLi	Et_2O	55	71	
5			THF	42	33	
6	**3b**	**6** 	Et_2O	79	52	**11**
7	**3b**		THF	72	74	
8	**3c**		Et_2O	46	66	
9	**3c**		THF	54	2	
10	**3b**	**7** 	Et_2O	70	68	**12**
11	**3b**		THF	75	97	
12	**3c**		Et_2O	79	83	
13	**3c**		THF	85	64	
14	**3b**	**8** 	Et_2O	86	34	**13**
15	**3b**		THF	86	61	
16	**3c**		Et_2O	89	72	
17	**3c**		THF	76	73	
18	**3b**	**9** 	Et_2O	85	9	**14**
19	**3b**		THF	56	6	
20	**3c**		Et_2O	91	81	
21	**3c**		THF	87	92	
22	**3b**	**10** 	Et_2O	67	80	**15**
23	**3b**		THF	95	85	
24	**3c**		Et_2O	86	79	
25	**3c**		THF	66	46	

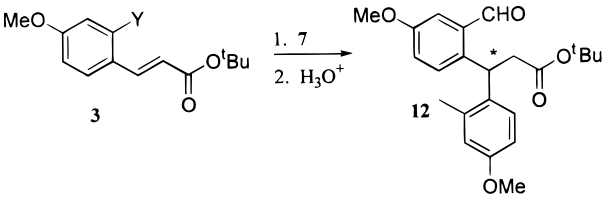
[a] Reactions were run with 2 equiv of ArLi in Et_2O/THF at −78 °C for 1 h or with 2 equiv of Ph_2CuLi at 0 °C. [b] PhLi was obtained as a 1.8 M solution in cyclohexanes−ether. Aryllithium reagents **6**−**10** were generated by reaction of the corresponding aryl bromide with 2 equiv of *t*-BuLi in Et_2O/THF at −78 °C. [c] Isolated yields of pure products after silica gel chromatography. The yields are for three steps: protection, 1,4-addition, and deprotection. See Experimental Section. [d] The ee was measured by supercritical fluid chromatography on purified samples. Stationary phases dependent on substrate. See Experimental Section.

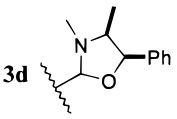
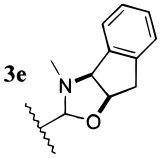
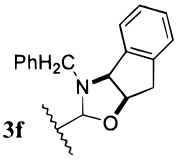
oxazolidines **3c**−**f** (derived from (1*S*,2*S*)-pseudoephedrine, (1*S*,2*R*)-ephedrine, (1*R*,2*S*)-*cis*-1-methylamino-2-indanol, and (1*R*,2*S*)-*cis*-1-benzylamino-2-indanol, respectively) were reacted with aryllithium reagent **7** using

(17) Less than 5% of 1,2-addition products as measured by ^{1}H NMR (represents the total of 1,2-addition product, 1,2-1,4-over addition product, and 1,2-1,2-over addition product).

(18) The surprisingly low stereoselectivity observed in the reaction of **3b** with Ph_2CuLi in Et_2O is the result of an electronic effect in the cuprate chemistry. The same reaction involving desmethoxy **3b** proceeded with high stereoselectivity (90% ee), in accordance with the literature precedent.[8] Interestingly, the aryllithium chemistry does not show this electronic effect, since the reactions of phenyllithium with **3b** and with desmethoxy **3b** proceeded with similar stereoselectivity (48% ee and 38% ee, respectively).

Table 2. Reactions[a] of Aryllithium 7 with Oxazolidines 3



Entry	3	Solvent	Yield (%)[b]	ee (%)
1	**3c**	Et_2O	79	83
2	**3c**	THF	85	64
3	 **3d**	Et_2O	87	63
4	**3d**	THF	90	12
5	 **3e**	Et_2O	64	40
6	**3e**	THF	87	31
7	 **3f**	Et_2O	68	9
8	**3f**	THF	68	8

[a] Reactions were run with 2 equiv of ArLi in Et_2O/THF at −78 °C for 1 h. [b] Isolated yields of pure products after silica gel chromatography. The yields are for three steps: protection, 1,4-addition, and deprotection. See Experimental Section.

both Et_2O and THF as the solvent (Table 2). In each case, the yields of 1,4-adduct **12** were high, and the enantioselectivities were found to be dependent on the structure of the oxazolidine and on the solvent. Interestingly, a general trend was again observed (consistent with the data in Table 1) for optimal enantioselectivities being obtained in the reactions of the oxazolidines **3c**−**f** in Et_2O as the solvent (entries 1, 3, 5, and 7). The best result was obtained using the (1*S*,2*S*)-pseudoephedrine-based oxazolidine **3c** in Et_2O (entry 1). These results are in general agreement with the model proposed by Alexakis (for the cuprate reactions) in which the conformation of the unsaturated ester, relative to the chiral auxiliary, is important for high stereoselectivity. It is likely that the oxazolidines **3c**−**f** have quite different conformational preferences, resulting in the observed variation in reaction stereoselectivity.

To further probe the importance of substrate conformation on the reaction stereoselectivity, the reactions of aryllithium reagents with the α,β-unsaturated esters **16b/16c**, which bear an *o*-methyl substituent, were studied (Scheme 2).[19] It was predicted that these substrates would have different conformational preferences

(19) **16a** was prepared from 2-bromo-3-methylbenzaldehyde and *tert*-butyl acrylate, via Heck reaction: see Experimental Section.

Scheme 2

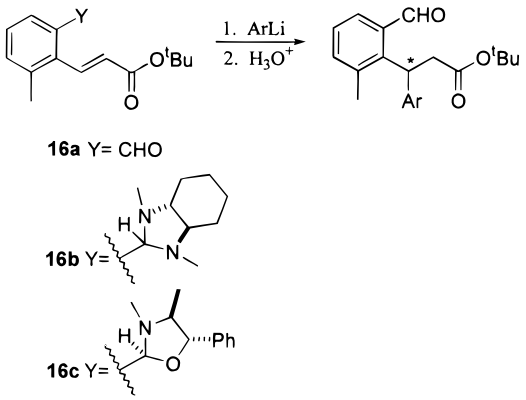


Table 3. Reactions[a] of Aryllithium Reagents with Acceptors 16b/16c

entry	16	ArLi	solvent	yield (%)[b]	ee (%)	product
1	**16b**	**6**	THF	54	45	**17**
2	**16c**		Et_2O	45	93	
3	**16b**	**7**	THF	76	54	**18**
4	**16c**		Et_2O	73	95	
5	**16b**	**8**	THF	85	57	**19**
6	**16c**		Et_2O	78	84	
7	**16b**	**9**	THF	94	74	**20**
8	**16c**		Et_2O	95	72	

[a] Reactions were run with 2 equiv of ArLi in Et_2O/THF at −78 °C for 1 h. [b] Isolated yields of pure products after silica gel chromatography. The yields are for three steps: protection, 1,4-addition, and deprotection. See Experimental Section.

to unsaturated esters **3b/3c** and might behave differently in this 1,4-addition chemistry. Thus, **16b/16c** were reacted with aryllithium reagents **6**−**9**, using THF as the solvent for reactions of imidazolidine **16b** and Et_2O as the solvent for reactions involving oxazolidine **16c** (Table 3). On the basis of our earlier observations (Tables 1 and 2), these solvent−auxiliary combinations were expected to provide optimal enantioselectivities. Several points should be made regarding the data in Table 3. First, in each case, the 1,4-adducts **17**−**20** were obtained cleanly and efficiently with minimal 1,2-addition.[20] Also, for each aryllithium reagent, the **16c**−Et_2O combination provided the 1,4-adducts with higher enantioselectivities (up to 95% ee) than the **16b**−THF combination. This is in contrast to the 1,4-addition reactions of **3b/3c**, which are more sensitive to the nature of the aryllithium reagent. It is speculated that, for **16b/16c**, the substrate conformation overrides contributions from the aryllithium reagent (steric effects, aggregation phenomena) in determining the stereoselectivities, while, for **3b/3c**, the stereoselectivities arise from a subtle balance of these effects.

In summary, it has been shown that aryllithium reagents react rapidly and efficiently with β-aryl-α,β-unsaturated *tert*-butyl esters bearing a chiral imidazolidine or oxazolidine to give the 1,4-addition products in high yield and optical purity. This chemistry is practical,[21] utilizes readily available and inexpensive chiral

(20) The absolute configurations of these 1,4-addition products were not determined. Either product enantiomer can be prepared by using the appropriate enantiomer of pseudoephedrine/bis-*N*-methylamino cyclohexane, both of which are readily available.

(21) This reaction can be perfomed on a multigram scale. For example, the 1,4-addition of **9** to **3c** in THF was carried out on a 5-g scale to give **14** in 87% isolated yield and 92% ee.

auxiliaries, and can be used to prepare a wide variety of structurally complex chiral β,β-diaryl propanoates. The levels of stereoselectivity observed in this process are dependent on the structure of the imidazolidine/oxazolidine, on the substitution in the acceptor/nucleophile, and on the solvent. For any given combination of aryllithium reagent and acceptor, optimal selectivities were obtained by matching the auxiliary and solvent effects.

Experimental Section

General Methods. All manipulations were carried out under a positive atmosphere of dry nitrogen. Dry THF and Et_2O were used (KF <150 μg/mL). NMR data was obtained in C_6D_6 from a Bruker AM300 spectrometer. Coupling constants are reported in hertz. Enantioselectivities were determined using supercritical fluid chromatography (Hewlett-Packard HP1205A SFC). All chemicals were procured from Aldrich Chemical Co. and were used without further purification. 2-Bromo-5-methoxybenzaldehyde was prepared from methyl-2-bromo-5-methoxybenzoate via DIBAL reduction[22] followed by PCC oxidation.[23] 2-Bromo-3-methylbenzaldehyde was prepared in 50% yield from 2-bromo-*m*-xylene by a published procedure.[24] (1*R*,2*R*)-bis-*N*-methylamino cyclohexane was prepared from (1*R*,2*R*)-*N*,*N*-cyclohexanediamine by a published procedure.[25] (1*R*,2*S*)-*cis*-1-Amino-2-indanol was used to prepare (1*R*,2*S*)-*cis*-1-methylamino-2-indanol[25] and (1*R*,2*S*)-*cis*-1-benzylamino-2-indanol.[26]

3-(2-Formyl-4-methoxyphenyl)-2-propenoic Acid 1,1-Dimethylethyl Ester (3a). To a solution of 2-bromo-5-methoxybenzaldehyde (2.49 g, 11.6 mmol) in toluene (40 mL) at 25 °C were added, successively, *tert*-butyl acrylate (2.55 mL, 17.4 mmol), NaOAc (2.85 g, 34.8 mmol), (o-tolyl)$_3$P (353 mg, 1.16 mmol), and (allyl)$_2$PdCl$_2$ (212 mg, 0.58 mmol), and the mixture was heated to reflux. After 8 h, the mixture was concentrated, and the crude product was purified by silica gel chromatography (eluted with hexanes/EtOAc) to give **3a** (2.43 g, 80% yield): ^{1}H NMR (C_6D_6) δ 9.93 (s, 1H), 8.61 (d, J = 15.7, 1H), 7.07 (m, 2H), 6.65 (dd, J = 2.8, 8.6, 1H), 6.28 (d, J = 15.7, 1H), 3.13 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (C_6D_6) δ 190.0, 165.6, 161.0, 139.0, 135.5, 129.2, 123.3, 120.7, 114.1, 80.1, 54.9, 28.2; HR-MS calcd for $C_{15}H_{18}O_4$ m/z 262.1205, found m/z 262.1211.

3-(2-Formyl-6-methylphenyl)-2-propenoic acid 1,1-dimethylethyl ester (16a): prepared using the procedure described above and starting with 2-bromo-3-methylbenzaldehyde. **16a** was obtained in 78% yield: ^{1}H NMR (C_6D_6) δ 10.01 (s, 1H), 7.88 (d, J = 16.0, 1H), 7.70 (dd, J = 1.6, 7.0, 1H), 6.85 (m, 2H), 5.76 (d, J = 16.1, 1H), 1.88 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (C_6D_6) δ 190.7, 164.7, 139.4, 138.1, 137.5, 135.3, 135.0, 129.6, 128.4, 126.9, 80.5, 28.1, 19.6; HR-MS calcd for $C_{15}H_{18}O_3$ m/z 246.1256, found m/z 246.1262.

General Procedure A. 1,4-Addition Reaction Involving Imidazolidines. Preparation of 2-Formyl-4-methoxy-β-(4-methoxyphenyl)benzenepropanoic Acid 1,1-Dimethylethyl Ester (11). To a solution of **3a** (312 mg, 1.19 mmol) in CH_2Cl_2 (5 mL) at 25 °C were added (1*R*,2*R*)-bis-*N*-methylamino cyclohexane (169 mg, 1.19 mmol) and 4 Å powdered molecular sieves (140 mg). After 3 h, the mixture was filtered and washed with CH_2Cl_2, and the solvent was evaporated to give **3b** (460 mg) as an oil. To a cold (−78 °C) solution of 4-bromoanisole (0.30 mL, 2.38 mmol) in THF (7 mL) was added *tert*-BuLi (1.7 M solution in pentane, 2.80 mL, 4.76 mmol), maintaining the temperature below −70 °C. After the mixture was aged for 1 h, a solution of **3b** (460 mg, 1.19 mmol) in THF (7 mL) was added, maintaining the reaction temperature below −70 °C. After being aged for 1 h, the mixture was quenched into saturated aqueous NH_4Cl (25 mL), EtOAc (25 mL) was added, and the layers were separated. The aqueous phase was extracted with EtOAc (10 mL), and the organic phases were combined, washed with brine (25 mL), and concentrated. The mixture was dissolved in THF (3 mL), water (0.8 mL), and HOAc (1.7 mL), and the solution was stirred at 25 °C for 1 h. The mixture was diluted with water (25 mL) and EtOAc (25 mL), the layers were separated, and the aqueous phase was extracted with EtOAc (10 mL). The combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel chromatography (eluted with toluene/EtOAc) to give **11** (317 mg, 72% yield, 74% ee). The same procedure was followed using Et_2O as the solvent for the 1,4-addition reaction to give **11** in 79% yield and 52% ee: ^{1}H NMR (C_6D_6) δ 10.42 (s, 1H), 7.31 (d, J = 2.8, 1H), 7.10 (d, J = 8.6, 1H), 7.03 (d, J = 8.6, 2H), 6.85 (dd, J = 2.8, 8.5, 1H), 6.70 (d, J = 8.6, 2H), 5.57 (t, J = 8.1, 1H), 3.29 (s, 1H), 3.23 (s, 1H), 2.87 (d, J = 8.2, 2H), 1.24 (s, 9H); ^{13}C NMR (C_6D_6) δ 190.9, 170.4, 158.7, 138.8, 136.0, 135.2, 129.7, 129.2, 120.8, 114.3, 114.2, 80.1, 54.8, 54.7, 42.6, 39.6, 27.9; HR-MS calcd for $C_{22}H_{26}O_5$ m/z 370.1780, found m/z 370.1812. Enantioselectivity data was determined by SFC using a Chiralcel OD(H) column at 35 °C, 300 bar, and 1 mL/min and with MeOH as the modifier.

General procedure B. 1,4-Addition Reaction Involving Oxazolidines. Preparation of (11). To a solution of **3a** (270 mg, 1.15 mmol) in toluene (8 mL) were added (1*S*,2*S*)-pseudoephedrine (209 mg, 1.27 mmol) and 1 drop of concd HCl, and the mixture was refluxed for 3.5 h. The mixture was quenched into saturated aqueous $NaHCO_3$ (15 mL), EtOAc (10 mL) was added, and the organic phase was washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to give **3c** (422 mg) as an oil. To a cold (−78 °C) solution of 4-bromoanisole (0.26 mL, 2.07 mmol) in Et_2O (7 mL) was added *tert*-BuLi (1.7 M solution in pentane, 2.42 mL, 4.15 mmol), maintaining the temperature below −70 °C. After this mixture was aged for 1 h, a solution of **3c** (422 mg, 1.03 mmol) in Et_2O (7 mL) was added, maintaining the reaction temperature below −70 °C. After being aged for 1 h, the mixture was quenched into saturated aqueous NH_4Cl (25 mL), EtOAc (25 mL) was added, and the layers were separated. The aqueous phase was extracted with EtOAc (10 mL), and the organic phases were combined, washed with brine (25 mL), and concentrated. The mixture was dissolved in THF (3 mL), water (0.8 mL), and HOAc (1.7 mL), and the solution was stirred at 25 °C for 1 h. The mixture was diluted with water (25 mL) and EtOAc (25 mL), the layers were separated, and the aqueous phase was extracted with EtOAc (10 mL). The combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel chromatography (eluted with toluene/EtOAc) to give **11** (203 mg, 46% yield, 66% ee). The same procedure was followed using THF as solvent for the 1,4-addition reaction to give **11** in 54% yield and 2% ee.

The following compounds were prepared by either general procedure A or B. Yields and enantioselectivities are listed in Tables 1−3. Spectral data is given below.

2-Formyl-4-methoxy-β-phenylbenzenepropanoic acid 1,1-dimethylethyl ester (5): prepared using a commercially available solution of PhLi (1.8 M in cyclohexanes−ether); ^{1}H NMR (C_6D_6) δ 10.36 (s, 1H), 7.29 (d, J = 2.9, 1H), 7.07 (m, 6H), 6.80 (dd, J = 2.9, 8.6, 1H), 5.61 (t, J = 8.1, 1H), 3.19 (s, 3H), 2.85 (m, 2H), 1.22 (s, 9H); ^{13}C NMR (C_6D_6) δ 190.9, 170.3, 158.7, 144.0, 138.3, 135.2, 129.8, 128.8, 128.2, 126.7, 120.8, 114.4, 80.2, 54.8, 42.4, 40.3, 27.9; HR-MS calcd for $C_{21}H_{24}O_4$ m/z 340.1674, found m/z 340.1667. Enantioselectivity data was determined by SFC using three Chiralpak AS columns in sequence at 35 °C, 200 bar, and 1 mL/min and with MeOH as the modifier.

2-Formyl-4-methoxy-β-(4-methoxy-2-methylphenyl)benzenepropanoic acid 1,1-dimethylethyl ester (12): ^{1}H NMR (C_6D_6) δ 10.40 (s, 1H), 7.32 (d, J = 2.8, 1H), 7.08 (m, 2H) 6.78 (dd, J = 2.7, 8.6, 1H), 6.67, (m, 2H), 5.70, (t, J = 7.9, 1H), 3.38 (s, 3H), 3.29 (s, 3H), 2.84 (m, 2H), 2.08 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (C_6D_6) δ 191.2, 170.6, 158.7, 158.6, 138.2, 137.9, 134.9, 133.8, 130.4, 120.5, 116.8, 115.0, 111.3, 80.1, 54.9, 54.7, 42.5, 36.8, 27.9, 19.8; HR-MS calcd for $C_{23}H_{28}O_5$ m/z 384.1937, found m/z 384.1959. Enantioselectivity data was determined by SFC

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using a Chiralcel OD(H) column at 35 °C, 300 bar, and 1 mL/min and with MeOH as the modifier.

2-Formyl-4-methoxy-*β*-[2-(1-methylethyl)phenyl]benzenepropanoic acid 1,1-dimethylethyl ester (13): ^{1}H NMR (C_6D_6) δ 10.36 (s, 1H), 7.26 (m, 2H), 7.12 (m, 3H), 7.00 (d, J =8.7, 1H), 6.66 (dd, J = 2.9, 8.7, 1H), 6.12 (t, J = 8.0, 1H), 3.30 (m, 1H), 3.18 (s, 3H), 2.92 (dd, J = 2.9, 8.0, 2H), 1.24 (s, 9H), 1.23 (d, J = 8.2, 3H), 0.90 (d, J = 6.8, 3H); ^{13}C NMR (C_6D_6) δ 191.3, 170.4, 158.6, 147.4, 139.7, 138.7, 134.5, 130.9, 127.4, 127.3, 126.4, 125.8, 120.3, 116.1, 80.2, 54.8, 42.9, 36.8, 28.8, 27.9, 24.4, 23.4; HR-MS calcd for $C_{20}H_{22}O_4$ (M + $-C_4H_8$) m/z 326.1518, found m/z 326.1489. Enantioselectivity data was determined by SFC using two Chiralcel OD(H) columns in sequence at 35 °C, 200 bar, and 1 mL/min and with *i*PrOH as the modifier.

***β*-(2-Formyl-4-methoxyphenyl)[1,1′-biphenyl]-2-propanoic acid 1,1-dimethylethyl ester (14)**: ^{1}H NMR (C_6D_6) δ 9.75 (s, 1H), 7.37 (d, J = 7.7, 1H), 7.28 (d, J = 2.9, 1H), 7.20 (m, 1H), 7.06 (m, 8H), 6.75 (dd, J = 2.9, 8.7, 1H), 5.73 (t, J = 8.0, 1H), 3.23 (s, 3H), 2.84 (m, 2H), 1.20 (s, 9H); ^{13}C NMR (C_6D_6) δ 189.6, 170.3, 158.4, 143.2, 141.5, 140.6, 138.6, 134.8, 130.8, 130.6, 129.4, 128.5, 127.5, 127.0, 126.8, 121.0, 112.0, 80.3, 54.8, 42.7, 36.9, 27.9; HR-MS calcd for $C_{27}H_{28}O_4$ m/z 416.1987, found m/z 416.1986. Enantioselectivity data was determined by SFC using a Chiralcel OD(H) column at 35 °C, 300 bar, and 1 mL/min and with *i*-PrOH as the modifier.

***β*-(2-Formyl-4-methoxyphenyl)-1-naphthalenepropanoic acid 1,1-dimethylethyl ester (15)**: ^{1}H NMR (C_6D_6) δ 10.34 (s, 1H), 8.25 (d, J = 8.0, 1H), 7.62 (d, J = 7.3, 1H), 7.59 (d, J = 8.2, 1H), 7.24 (m, 5H), 7.06 (d, J = 8.6, 1H), 6.62 (m, 2H), 3.19 (s, 3H), 3.00 (m, 2H), 1.21 (s, 9H); ^{13}C NMR (C_6D_6) δ 191.5, 170.5, 158.7, 139.8, 137.8, 134.8, 134.6, 131.9, 130.3, 129.2, 127.9, 126.8, 125.9, 125.4, 125.2, 123.9, 120.2, 116.4, 80.2, 54.8, 42.4, 37.1, 27.9; HR-MS calcd for $C_{25}H_{26}O_4$ m/z 390.1831, found m/z 390.1837. Enantioselectivity data was determined by SFC using a Chiralcel OD(H) column at 35 °C, 300 bar, and 1 mL/min and with *i*-PrOH as the modifier.

2-Formyl-*β*-(4-methoxyphenyl)-6-methylbenzenepropanoic acid 1,1-dimethylethyl ester (17): ^{1}H NMR (C_6D_6) δ 10.30 (s, 1H), 7.81 (d, J = 7.2, 1H), 6.99 (m, 2H), 6.88 (d, J = 8.5, 2H), 6.64 (d, J = 8.7, 2H), 5.45 (m, 1H), 3.31 (s, 3H), 3.08 (dd, J = 7.4, 14.7, 1H), 2.73 (dd, J = 8.6, 14.7, 1H), 2.16 (s, 3H), 1.19 (s, 9H); ^{13}C NMR (C_6D_6) δ 191.5, 171.0, 158.4, 144.5, 138.7, 136.4, 135.0, 128.5, 127.9, 127.2, 114.3, 80.3, 54.7, 41.0, 38.6, 27.8, 20.7; HR-MS calcd for $C_{18}H_{18}O_4$ (M + $-C_4H_8$) m/z 298.1205, found m/z 298.1182. Enantioselectivity data was determined by SFC using a Chiralcel OD(H) column at 35 °C, 300 bar, and 1 mL/min and with *i*-PrOH as the modifier.

2-Formyl-*β*-(4-methoxy-2-methylphenyl)-6-methylbenzenepropanoic acid 1,1-dimethylethyl ester (18): ^{1}H NMR (C_6D_6) δ 10.34 (s, 1H), 7.65 (d, J = 6.3, 1H), 7.28 (d, J = 8.5, 1H), 6.92 (m, 2H), 6.63 (d, J = 6.6, 1H), 6.55 (s, 1H), 5.36 (m, 1H), 3.34 (s, 3H), 3.13 (dd, J = 10.0, 15.4, 1H), 2.65 (dd, J = 5.5, 15.5, 1H), 2.12 (s, 3H), 1.69 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (C_6D_6) δ 191.4, 170.7, 158.8, 144.3, 138.6, 137.8, 136.5, 136.4, 132.9, 128.7, 127.0, 117.3, 110.9, 80.4, 54.7, 40.2, 39.1, 27.9, 20.8, 20.2; HR-MS calcd for $C_{23}H_{28}O_4$ m/z 368.1987, found m/z 368.2014. Enantioselectivity data was determined by SFC using a Chiralcel OD(H) column at 35 °C, 300 bar, and 1 mL/min and with *i*-PrOH as the modifier.

2-Formyl-6-methyl-*β*-[2-(1-methylethyl)phenyl]benzenepropanoic acid 1,1-dimethylethyl ester (19): ^{1}H NMR (C_6D_6) δ 10.31 (s, 1H), 7.64 (m, 1H), 7.40 (d, J = 7.7, 1H), 7.08 (d, J = 4.0, 2H), 7.03 (m, 1H), 6.91 (m, 2H), 5.72 (m, 1H), 3.15 (dd, J = 10.2, 15.8, 1H), 2.88 (m, 1H), 2.67 (dd, J = 5.6, 15.8, 1H), 2.09 (s, 3H), 1.26 (s, 9H), 1.07 (d, J = 6.8, 3H), 0.64 (d, J = 6.7, 3H); ^{13}C NMR (C_6D_6) δ 191.5, 170.5, 147.8, 144.8, 138.8, 137.7, 136.5, 129.3, 127.6, 127.3, 127.0, 126.6, 125.7, 80.4, 40.3, 39.0, 29.0, 27.9, 24.6, 22.8, 20.9; HR-MS calcd for $C_{24}H_{30}O_3$ m/z 366.2195, found m/z 366.2194. Enantioselectivity data was determined by SFC using a Chiralcel OD(H) column at 35 °C, 300 bar, and 1 mL/min and with *i*-PrOH as the modifier.

***β*-(2-Formyl-6-methylphenyl)[1,1′-biphenyl]-2-propanoic acid 1,1-dimethylethyl ester (20)**: ^{1}H NMR (C_6D_6) δ 10.00 (s, 1H), 7.49 (d, J = 7.9, 1H), 7.42 (d, J = 7.3, 1H), 7.14 (m, 1H), 7.02 (m, 2H), 6.78 (m, 7H), 5.74 (m, 1H), 3.17 (dd, J = 10.4, 15.8, 1H), 2.62 (dd, J = 5.3, 15.9, 1H), 1.74 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (C_6D_6) δ 191.0, 170.7, 144.2, 143.5, 142.3, 140.4, 138.0, 136.3, 135.9, 131.1, 128.8, 128.7, 128.5, 127.9, 127.3, 127.2, 126.7, 126.6, 80.3, 39.2, 38.9, 27.9, 20.6; HR-MS calcd for $C_{23}H_{20}O_3$ (M + $-C_4H_8$) m/z 344.1412, found m/z 344.1429. Enantioselectivity data was determined by SFC using a Chiralcel OD(H) column at 35 °C, 300 bar, and 1 mL/min and with *i*-PrOH as the modifier.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **3a**, **5**, **11**−**15**, **16a**, and **17**−**20** (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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