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Asymmetric Synthesis of Carboxylic Acid Derivatives Having an All-Carbon α-Quaternary Center through Cu-Catalyzed 1,4-Addition of Dialkylzinc Reagents to 2-Aryl Acetate Derivatives

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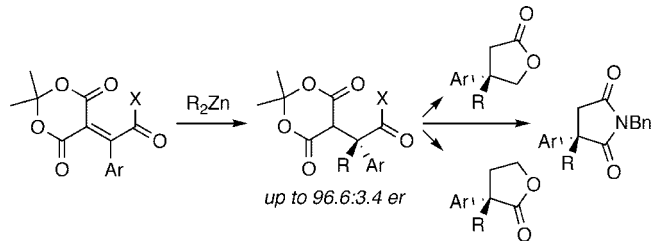
ABSTRACT



The asymmetric synthesis of carboxylic acid derivatives having an all-carbon α-quaternary center has been achieved via copper-catalyzed 1,4-addition of dialkylzinc reagents to aryl acetate derivatives in the presence of phosphoramidite ligand. High isolated yields and enantioselectivities were obtained. It was demonstrated that the Meldrum's acid and ester moieties present on the all-carbon quaternary center allow for a wide variety of subsequent transformations, leading to the expedient preparation of succinimides, succinate esters and succinic acids, γ-butyrolactones, and β-amino acid derivatives.

Asymmetric synthesis of carboxylic acid derivatives having an all-carbon α-quaternary center is a long-standing challenge in organic chemistry. At present, only a handful of catalytic methods are available to access this structural motif.[1,2] Our recent success in the preparation of carboxylic acids having an all-carbon β-quaternary center by enantioselective conjugate addition[3,4] of dialkylzinc reagents to 5-(1-arylalkylidene) Meldrum's acids[5] encouraged us to broaden the scope and the synthetic versatility of this strategy. Consequently, we hypothesized that acyclic, tetrasubstituted olefins **1** might be suitable precursors to carboxylic acid derivatives bearing an all-carbon α-quaternary center. To the best of our knowledge, only two reports describe the synthesis of all-carbon quaternary center α to carbonyl groups in the context of asymmetric conjugate addition. Cu-catalyzed addition of organozinc reagents to cyclic γ-keto esters[6] and Rh-catalyzed

(1) For reviews on catalytic methods to all-carbon quaternary centers, see: (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363–5367.

(2) For recent examples, see: (a) Fujimoto, T.; Endo, K.; Tsuji, H.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 4492–4496. (b) Capuzzi, M.; Perdicchia, D.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 128–135. (c) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810–811. (d) Wiedemann, S. H.; Noda, H.; Harada, S.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 1661–1664. (e) Denmark, S. E.; Wilson, T. W.; Burk, M. T.; Heemstra, J. R., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 14864–14865. (f) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548–14549. (g) Doyle, A. G.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 3701–3705.

(3) For recent reviews on asymmetric conjugate addition, see: (a) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969–5994. (b) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279–1300.

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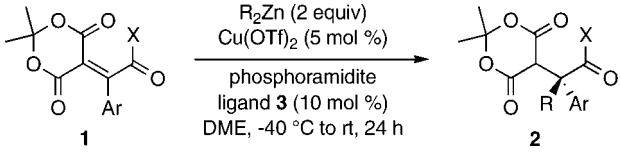
reaction of arylboronic acids with 3-substituted maleimides and 2-methyl-1,4-naphthoquinone[7] were described. In both these reports, excellent yields and selectivities were obtained on cyclic, trisubstituted olefins.

In this paper, we describe a general approach to the asymmetric construction of carboxylic acid derivatives having an all-carbon α-quaternary center via copper-catalyzed conjugate addition of dialkylzinc reagents to 2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)aryl acetates (**1**). As depicted in Scheme 1, the proposed general strategy relies

Scheme 1. General Strategy



on the highly activated nature of these Michael acceptors to induce umpolung of the position α to the non-Meldrum's acid carbonyl, and allow this center to act as an electrophile toward organozinc reagents.

Readily prepared[8] olefin **1a** was subjected to 2 equiv of Et_2Zn, 10 mol % of phosphoramidite ligand **3a**,[9] and 5 mol % of $Cu(OTf)_2$ in 1,2-dimethoxyethane (DME); **2a** was isolated as a single regioisomer in quantitative yield and an enantiomeric ratio of 94:6 (Table 1, entry 1). This result was gratifying as it represents the first example of enantioselective 1,4-addition to electrophilic sp^2-carbon centers flanked by two sp^2-hybridized carbons. In attempts to achieve higher selectivities, phosphoramidites **3b**−**f** were prepared (Figure 1).[10] It was found that the replacement of the phenyl group on **3a** with 2-naphthyl or cyclohexyl had little effect (entries 2 and 3). Similarly, analogous ethyl-substituted ligand **3d** furnished identical er as **3a** (entry 4). On the other hand, the

Table 1. Survey of Phosphoramidites Ligands **3** on the Addition of Et_2Zn to Alkene **1a**

entry	Ar	X	ligand	R	yield (%)	er (*S*:*R*)
1	C_6H_5	MeO (**1a**)	**3a**	Et (**2a**)	quant	94:6
2	C_6H_5	MeO (**1a**)	**3b**	Et (**2a**)	quant	95:5
3	C_6H_5	MeO (**1a**)	**3c**	Et (**2a**)	quant	96:4
4	C_6H_5	MeO (**1a**)	**3d**	Et (**2a**)	85	94:6
5	C_6H_5	MeO (**1a**)	**3e**	Et (**2a**)	85	85:15
6	C_6H_5	MeO (**1a**)	**3f**	Et (**2a**)	85	42:58

chiral amine moiety was crucial for optimal selectivity; using **3e**, **2a** was obtained in a moderate 85:15 er (entry 5). Furthermore, the binaphthyl moiety was necessary to achieve high enantioselectivity as the biphenol based ligand **3f** led to a poor er (entry 6). On the basis of these results, **3a** was selected as the optimal ligand and used throughout this study.

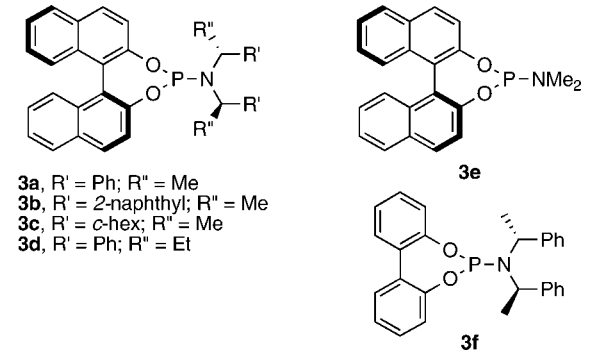


Figure 1. Phosphoramidite ligands **3a**−**f**.

We then set out to define the scope of the methodology by modifying the ester and aromatic moieties of **1** (Table 2). It was shown that the nature of the ester had modest influence on the enantioselectivity of the reaction (entries 1−6). Keeping the ester moiety constant (X = OMe), substitution at the para and meta positions of the phenyl ring was determined to have negligible influence on the enantioselectivity of the addition, regardless of the substituent steric demand and electronic nature, with er being highest in the para-substituted examples (entries 7−11 vs 12−14). Ortho substituents led to inconsistent results, as competing, racemic conjugate reduction occurred (**2**, R = H) and er fluctuated with the nature of the substituent (entries 15−18).[11] Furyl and naphthyl substrates **1s** and **1t** provided product **2s** and **2t**, respectively, in good yield and selectivity (entries 19 and 20).

(4) For synthesis of all-carbon quaternary centers via 1,4-addition to 3-substituted cyclic enones, see: (a) Palais, L.; Mikhel, I. S.; Bournaud, C.; Micouin, L.; Falciola, C. A.; Vuagnoux-d'Augustin, M.; Rosset, S.; Bernardinelli, G.; Alexakis, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7462–7465. (b) Vuagnoux-d'Augustin, M.; Kehrli, S.; Alexakis, A. *Synlett* **2007**, 2057–2060. (c) Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem. Eur. J.* **2007**, *13*, 9647–9662. (d) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417. (e) Lee, K.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184. (f) Fuchs, N.; d'Augustin, M.; Humam, M.; Alexakis, A.; Taras, R.; Gladiali, S. *Tetrahedron: Asymmetry* **2005**, *16*, 3143–3146. (g) Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988–14989. (h) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376–1378. For 1,4-addition to 2,2-disubstituted nitroolefins, see: (i) Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584–4585. For 1,4-addition to β,β-disubstituted α,β-unsaturated pyridylsulfones, see: (j) Mauleón, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961–4963.

(5) (a) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775. (b) Fillion, E.; Wilsily, A.; Liao, E.-T. *Tetrahedron: Asymmetry* **2006**, *17*, 2957–2959.

(6) Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097–1100.

(7) Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628–5629.

(8) Knoevenagel condensation of arylglyoxylates with Meldrum's acid, see: (a) Baxter, G. J.; Brown, R. F. C. *Aust. J. Chem.* **1975**, *28*, 1551–1557.

(9) (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353. (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620–2623.

(10) (a) Li, K.; Alexakis, A. *Tetrahedron Lett.* **2005**, *46*, 8019–8022. (b) Watanabe, T.; Knöpfel, T. F.; Carreira, E. M. *Org. Lett.* **2003**, *5*, 4557–4558. (c) Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillet, F.; Benhaim, C. *Synlett* **2001**, 1375–1378. (d) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865–2878. (e) Hulst, R.; de Vries, N. K.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 699–708.

Table 2. Influence of the Ester and Aryl Moieties on the Addition of Et_2Zn to **1**

entry	Ar	X	R	yield (%)	er (*S*:*R*)
1	C_6H_5	MeO (**1a**)	Et (**2a**)	quant	94:6
2	C_6H_5	EtO (**1b**)	Et (**2b**)	94	95:5
3	C_6H_5	*t*-BuO (**1c**)	Et (**2c**)	quant	93:7
4	C_6H_5	BnO (**1d**)	Et (**2d**)	98	94:6
5	C_6H_5	(allyl)O (**1e**)	Et (**2e**)	quant	94:6
6	C_6H_5	*t*-BuS (**1f**)	Et (**2f**)	90	95:5
7	4-ClC_6H_4	MeO (**1g**)	Et (**2g**)	91	97:3
8	4-BrC_6H_4	MeO (**1h**)	Et (**2h**)	97	96:4
9	4-MeC_6H_4	MeO (**1i**)	Et (**2i**)	98	95:5
10	4-*t*-BuC_6H_4	MeO (**1j**)	Et (**2j**)	82	96:4
11	4-$MeOC_6H_4$	MeO (**1k**)	Et (**2k**)	quant	96:4
12	3-ClC_6H_4	MeO (**1l**)	Et (**2l**)	92	91:9
13	3-MeC_6H_4	MeO (**1m**)	Et (**2m**)	quant	92:8
14	3-$MeOC_6H_4$	MeO (**1n**)	Et (**2n**)	87	91:9
15	2-ClC_6H_4	MeO (**1o**)	Et (**2o**)	41[a]	90:10
16	2-FC_6H_4	MeO (**1p**)	Et (**2p**)	62[b]	66:34
17	2-MeC_6H_4	MeO (**1q**)	Et (**2q**)	quant[c]	79:21
18	2-$MeOC_6H_4$	MeO (**1r**)	Et (**2r**)	79[d]	71:29
19	2-furyl	MeO (**1s**)	Et (**2s**)	97	94:6
20	2-naphthyl	MeO (**1t**)	Et (**2t**)	88	96:4

[a] Reduced product (R = H) isolated in 53% yield. [b] Reduced product (R = H) isolated in 12% yield. [c] Isolated as a 84:16 mixture of **2p** and reduced product (R = H). [d] Reduced product (R = H) isolated in 21% yield.

The addition of *n*-Bu_2Zn, *i*-Pr_2Zn, and Me_2Zn to alkylidenes **1g**, **1k**, and **1t** led to Meldrum's acids **2u**−**z** in er's up to 96:4 (Table 3).[12] *n*-Bu_2Zn and *i*-Pr_2Zn gave results

Table 3. Addition of Various Organozinc Reagents to Alkylidene **1**

entry	Ar	X	R	yield (%)	er (*S*:*R*)
1	4-$MeOC_6H_4$	MeO(**1k**)	*n*-Bu (**2u**)	91	95:5
2	2-naphthyl	MeO (**1t**)	*n*-Bu (**2v**)	88	96:4
3	4-$MeOC_6H_4$	MeO(**1k**)	*i*-Pr(**2w**)	86	92:8
4	2-naphthyl	MeO (**1t**)	*i*-Pr (**2x**)	79	94:6
5	4-ClC_6H_4	MeO(**1g**)	Me (**2y**)	quant	80:20
6	2-naphthyl	MeO (**1t**)	Me (**2z**)	90	81:19

comparable to Et_2Zn, but Me_2Zn furnished lower enantioselectivity.[13]

Insights into factors determining the enantioselectivity of the 1,4-addition were gained by solving the X-ray structure of **1t**. Figure 2 shows that the carbonyl group of the ester is nearly perpendicular to the alkene (dihedral angle C3−C7−C8−O5 = 101.5°),[14] which suggests that the nonplanar

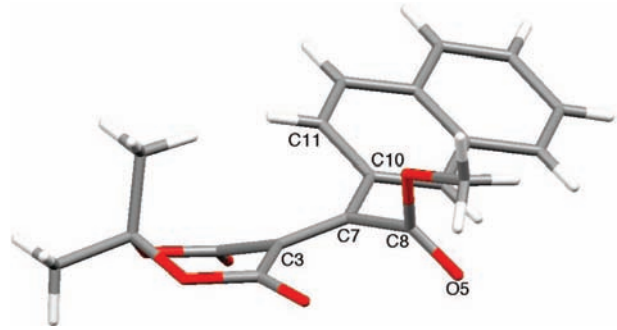
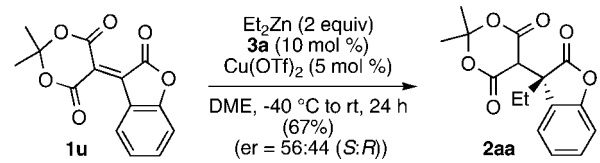


Figure 2. X-ray structure of alkylidene **1t**.

environment around the electrophilic carbon center created by the ester group's orientation might be key in the enantiodifferentiating step.

Our hypothesis was corroborated with conformationally locked and planar alkylidene **1u**. As shown in Scheme 2,

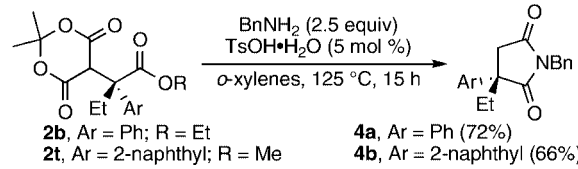
Scheme 2. Addition of Et_2Zn to Conformationally Locked and Planar Alkylidene **1u**



the addition of Et_2Zn furnished nearly racemic **2aa**, which contrasts with the selectivity obtained with nonplanar ortho substituted substrates **1o**−**r**.

The significance of preparing highly functionalized all-carbon quaternary centers **2** lies in the variety of subsequent transformations and diversity of chiral structures accessible through these intermediates. Chiral succinimides **4a** and **4b** were prepared in one step by treating **2b** and **2t**, respectively, with $BnNH_2$ (Scheme 3). This one-pot sequence allowed the

Scheme 3. Synthesis of Chiral Succinimides



establishement of the absolute stereochemistry for conjugate addition product **2** by comparison of known succinimides **4a** and **4b**.[7]

From compound **2d**, 3,3- and 4,4-disubstituted γ-butyrolactones **6a** and **6c** were readily accessed (Scheme 4). The

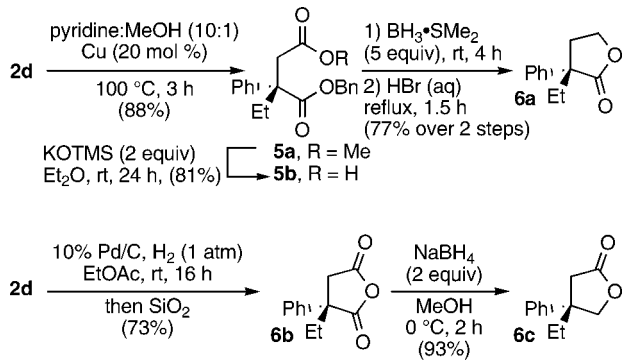
(11) The use of 10 equiv of styrene as an additive had no influence on the enantioselectivity or yield, see: Li, K.; Alexakis, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7600–7603.

(12) Addition of Ph_2Zn led to complex mixtures, in which the reduced product was major.

(13) A variety of reaction conditions were tested to improve the er for Me_2Zn addition. See the Supporting Information for details.

(14) Compared to 37.3° (C3−C7−C10−C11) for the naphthyl group.

Scheme 4. Synthesis of γ-Butyrolactones

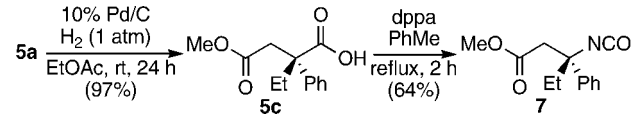


more reactive Meldrum's acid moiety found in **2d** could be transformed chemoselectively to provide **5a**. From diester **5a**, γ-butyrolactone **6a** was synthesized in three high-yielding steps. Disubstituted γ-butyrolactone **6c** was obtained in only two steps by hydrogenolysis of **2d** to anhydride **6b**, which was selectively reduced with $NaBH_4$ to give **6c**/**6a** in an excellent 18:1 ratio.

β-Amino acid derivative **7** was prepared through the deprotection of **5a**, followed by Curtius rearrangement of succinic acid derivative **5c** (Scheme 5).

In conclusion, we have described a highly enantioselective asymmetric synthesis of carboxylic acid derivatives having an all-carbon α-quaternary center through Cu-catalyzed 1,4-addition of dialkylzinc reagents to aryl acetate derivatives.

Scheme 5. β-Amino Acid Derivative Synthesis



This method employs commercially available ligand **3a** and readily accessible Meldrum's acids **1**. The significance of this method was established by the expedient preparation of succinimides, γ-butyrolactones, and β-amino acid derivatives from Meldrum's acid **2**. Further efforts to expand the synthetic scope of alkylidene Meldrum's acids in asymmetric synthesis are underway.

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Supporting Information Available: Experimental procedures, NMR spectra, and CIF file for **1t**. This material is available free of charge via the Internet at http://pubs.acs.org.

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