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Asymmetric Synthesis of All-Carbon Benzylic Quaternary Stereocenters via Cu-Catalyzed Conjugate Addition of Dialkylzinc Reagents to 5-(1-Arylalkylidene) Meldrum's Acids

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All-carbon benzylic quaternary centers are ubiquitous motifs in natural products and pharmaceutical agents. Conjugate addition[1] of carbon nucleophiles to electron-deficient olefins is a direct entry into these structural elements.[2] Surprisingly, the asymmetric synthesis of all-carbon quaternary stereocenters through 1,4-addition, under catalytic or stoichiometric conditions, has received limited attention. The minimal number of literature examples may be attributed to the intrinsic poor reactivity of tri- and tetrasubstituted alkene acceptors.[3] Alexakis' group reported the enantioselective conjugate addition of trialkylaluminum reagents to 3-substituted cyclohexen-2-ones in the presence of copper catalysts.[4] Likewise, Hoveyda and co-workers described the synthesis of nitroalkanes bearing all-carbon benzylic quaternary stereogenic centers via Cu-catalyzed asymmetric conjugate addition of dialkylzinc reagents to nitroalkenes.[5]

Aryl Grignard and organocopper reagents add in a conjugate fashion to 5-(1-alkylalkylidene) Meldrum's acids affording all-carbon benzylic quaternary centers.[6] Although a single case of this strategy has been described, this element of structure has been obtained alternatively by 1,4-addition of alkyl Grignard reagents to 5-(1-arylalkylidene) Meldrum's acids.[7] Asymmetric versions of either of these approaches have not been reported.[8] 5-(1-Substituted alkylidene) Meldrum's acids are conveniently prepared by Knoevenagel condensation of Meldrum's acid with ketones, for which typical problems associated with the preparation of geometrically pure olefin acceptors are absent.[9] Furthermore, benzyl Meldrum's acids resulting from conjugate addition are synthetically useful intermediates that may be subsequently submitted to various transformations.[7,9,10] In this Communication, we disclose our results on the asymmetric synthesis of all-carbon benzylic quaternary stereocenters through Cu-catalyzed addition of dialkylzinc reagents to 5-(1-arylalkylidene) Meldrum's acids **1**.

The ability of commercially available phosphoramidite ligand[11] **3** to promote the addition of Et_2Zn to **1** was first examined (Scheme 1). 5-(1-Phenylethylidene) Meldrum's acid (**1a**) was employed to probe for optimum solvent and temperature. A >99% conversion[12] and a 95% isolated yield of **2a** were obtained when **1a** was reacted with 2 equiv of Et_2Zn, 5 mol % of $Cu(OTf)_2$, and 10 mol % of **3** in 1,2-dimethoxyethane (DME).[13,14] The conjugate addition was relatively slow and was carried out at room temperature for 48 h (Table 1, entry 1).[15]

With this promising lead in hand, we proceeded to investigate the scope of the catalytic conjugate addition reaction, and the results are summarized in Table 1. The primary intent was to gain insights on the steric and electronic properties of the tetrasubstituted olefin substituents and their respective role on the enantioselectivity and efficiency of the process. Replacing the phenyl group in **1** by 2-naphthyl or 2-furyl provided **2b** and **2c** in 95 and 91% ee, respectively (entries 2 and 3). Substituting the 4-position of the phenyl moiety seemed to have a significant and favorable impact on the enantioselectivity of the addition (entries 4 and 5). This observation was further confirmed with substrates **1f**−**i**, substituted with an electron-withdrawing group (entries 6−9), and substrate **1j**, substituted with an electron-donating benzyloxy group (entry 10), with enantiomeric excesses ranging from 92 to 95%.

Scheme 1

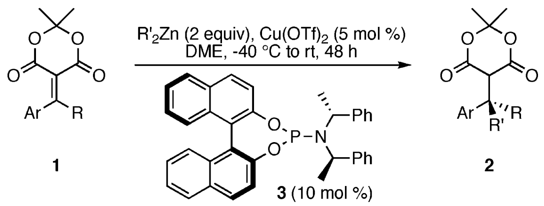

Table 1. Addition of R'_2Zn to 5-(1-Arylalkylidene) Meldrum's Acids

entry	Ar	R	R′	conv. (%)[a]	yield (%)	ee (%)[b]
1	Ph (**1a**)	Me	Et (**2a**)	>99	95	84
2	2-naphthyl (**1b**)	Me	Et (**2b**)	>99	66	95
3	2-furyl (**1c**)	Me	Et (**2c**)	>99	97	91
4	4-MePh (**1d**)	Me	Et (**2d**)	>99	82	89
5	4-PhPh (**1e**)	Me	Et (**2e**)	>99	76	95
6	4-ClPh (**1f**)	Me	Et (**2f**)	>99	88	95
7	4-BrPh (**1g**)	Me	Et (**2g**)	>99	84	92
8	4-FPh (**1h**)	Me	Et (**2h**)	>99	83	92
9	4-(F_3C)Ph (**1i**)	Me	Et (**2i**)	99	87	92
10	4-(BnO)Ph (**1j**)	Me	Et (**2j**)	92	75	93
11	3-MePh (**1k**)	Me	Et (**2k**)	96[c]	93	78
12	3-ClPh (**1l**)	Me	Et (**2l**)	99	96	74
13	3-(BnO)Ph (**1m**)	Me	Et (**2m**)	97	97	79
14	3,4-Cl_2Ph (**1n**)	Me	Et (**2n**)	99	98	85
15	2-MePh (**1o**)	Me	Et (**2o**)	0	NR	N/A
16	2-ClPh (**1p**)	Me	Et (**2p**)	0	NR	N/A
17	2-(BnO)Ph (**1q**)	Me	Et (**2q**)	0	NR	N/A
18	4-ClPh (**1r**)	*n*-Bu	Et (**2r**)	>99	78	94
19	Ph (**1s**)	*i*-Pr	Et (**2s**)	0	NR	N/A
20	4-ClPh (**1f**)	Me	*i*-Pr (**2t**)	>99	99	65
21	4-ClPh (**1t**)	Et	Me (**2f**)	35	N/A	N/A
22	4-ClPh (**1f**)	Me	*n*-Bu (**2u**)	99	87	87

[a] Determined by analysis of the crude ^1H NMR spectra. [b] Measured by HPLC using a Chiralcel OD, OD-H, or AD-H column. [c] Reaction time is 72 h.

Contrariwise, substituting the 3-position of the arene with electron-withdrawing or -donating groups had a detrimental effect on the enantioselectivity of the process (entries 11−13), and enantiomeric excesses of 74−79% were obtained. Of note, 5-(1-(3,4-dichlorophenyl)ethylidene) Meldrum's acid (**1n**) generated **2n** in 85% ee (entry 14). This result suggests that positions 3 and 4 of the phenyl group apparently offset one another, leading to an averaging of enantiomeric excess. Substrates bearing a substituent at the 2-position of the aromatic moiety withstand conjugate addition of Et_2Zn (entries 15−17). The close proximity of the aromatic substituent to the olefin electrophilic carbon likely blocks the

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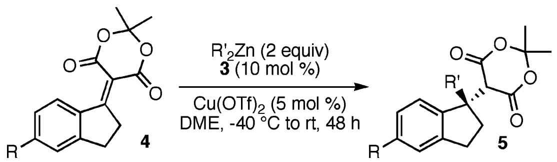
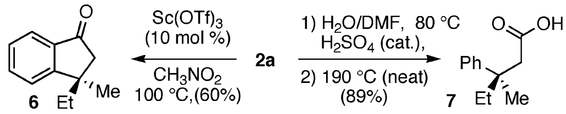
Table 2. Addition of R'_2Zn to 5-(Dihydroindenylidene) Meldrum's Acids



entry	R	R′	conv. (%)[a]	yield (%)	ee (%)[b]
1	H (**4a**)	Et (**5a**)	>99	96	96
2	Cl (**4b**)	Et (**5b**)	>99	94	99
3	Cl (**4b**)	Me (**5c**)	>99[c]	98	99
4	Cl (**4b**)	*n*-Bu (**5d**)	>99	97	97
5	Cl (**4b**)	*i*-Pr (**5e**)	>99	99	57

[a] Determined by analysis of the crude ^{1}H NMR spectra. [b] Measured by HPLC using a Chiralcel OD, OD-H, or AD-H column. [c] Five equivalents of Me_2Zn were used.

Scheme 2



trajectory for alkyl delivery, resulting in a lack of reactivity for **1o**, **1p**, and **1q**.

Increasing the length of the alkyl chain on the electrophilic carbon of the olefin acceptor did not affect enantioselectivity, as illustrated with pentylidene Meldrum's acid **1r** that furnished the addition product **2r** in 94% ee (entry 18). Sterically demanding substrate **1s** was unreactive toward Et_2Zn (entry 19). On the other hand, *i*-Pr_2Zn added efficiently to **1f**, albeit with a modest 65% ee (entry 20). Meldrum's acid **1t** displayed sluggish reactivity with Me_2Zn (entry 21), but the addition of *n*-Bu_2Zn to **1f** afforded **2u** in 87% yield and 87% ee (entry 22).

The asymmetric synthesis of 1,1-disubstituted chiral indanes **5** from Meldrum's acid derivatives **4** was also tackled (Table 2).[16] In all cases, conversion was >99%. As for substrates **1**, the introduction of a chloride group in **4** para (5-position) to the benzylic electrophilic site enhanced enantioselection (entries 1 and 2). A variety of dialkylzinc reagents (Et_2Zn, Me_2Zn, *n*-Bu_2Zn) added to **4b** with equal enantioselectivity (97−99%) and efficiency (94−99%) (entries 2−4), with the exception of *i*-Pr_2Zn, which gave **5e** in 57% ee (entry 5).

The synthetic utility of benzyl Meldrum's acids **2** was exemplified, and the absolute stereochemistry of the addition products was determined, by preparing known compounds **6** and **7** (Scheme 2). Using a protocol previously developed in our group,[10] **2a** was transformed into (*R*)-3-ethyl-3-methyl-1-indanone (**6**).[17] Hydrolysis of **2a** led to β,β-disubstituted pentanoic acid **7**.

In conclusion, we have described the first highly enantioselective synthesis of all-carbon benzylic quaternary stereocenters via conjugate addition of dialkylzinc reagents to readily accessible 5-(1-arylalkylidene) and 5-(dihydroindenylidene) Meldrum's acids **1** and **4**. This method employs commercially available ligand **3** and dialkylzinc reagents. The significance of substituting the position para, meta, and ortho to the electrophilic benzylic center was highlighted. Current efforts are centered at broadening the scope of enantioselective conjugate additions to 5-alkylidene Meldrum's acids.

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Supporting Information Available: Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Typically, R_f values of the product and starting material were comparable, thus the need for high % conversion to simplify purification.

(13) Meldrum's acid **2a** was formed in 86% yield (96% conversion) and 85% ee when **1a** was reacted with 2 equiv of Et_2Zn, 6 mol % of **3**, and 3 mol % of $Cu(OTf)_2$ in DME. Solvents typically used in Cu-catalyzed enantioselective conjugate additions, such as Et_2O (91%, 59% ee), THF (59%, 63% ee), and toluene (99%, 57% ee), were inferior. MTBE (62%, 53% ee) and 1,4-dioxane (21%, 36% ee) also furnished poor results.

(14) Comparable results were obtained with 5 mol % of $Cu(OAc)_2 \cdot H_2O$ (90%, 88% ee), $Cu(acac)_2 \cdot H_2O$ (91%, 88% ee), and $Cu(O_2CCF_3)_2 \cdot H_2O$ (99%, 88% ee), but CuCN gave **1a** in 80% yield and 48% ee.

(15) Adding various amounts of $Zn(OTf)_2$ to the reaction mixture showed no effect on either the enantioselectivity or the rate of the reaction; see ref 1b.

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