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Asymmetric Synthesis of All-Carbon Benzylic Quaternary Stereocenters via Conjugate Addition to Alkylidene and Indenylidene Meldrum's Acids

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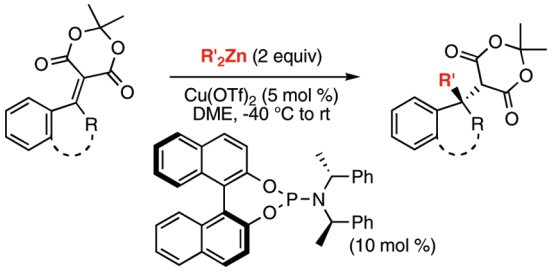

A systematic study outlining the enantioselective 1,4-addition of dialkylzinc reagents to 5-(1-arylalkylidene) and indenylidene Meldrum's acids is presented. Variation of the aryl and alkyl groups present on the alkylidene was thoroughly explored. The 1,4-addition displayed compatibility with a wide range of heteroaromatics and functional groups, and the arene pattern of substitution affected enantioselection, with a para-substituted aryl group consistently leading to high enantioselectivities. The nature of the organozinc reagent on the efficiency and selectivity of the conjugate addition was also investigated. The solid-state conformation was determined for a number of alkylidene Meldrum's acids and correlated with the observed enantioselectivity in relation to the arene pattern of substitution.

Introduction

The catalytic enantioselective conjugate addition of organometallic reagents to electron-deficient olefins ranks among the most versatile C−C bond-forming transformations in synthetic organic chemistry.[1] Despite the remarkable achievements in the asymmetric formation of tertiary stereocenters, the intrinsic poor reactivity of tri- and tetrasubstituted alkene acceptors has rendered the construction of all-carbon quaternary stereocenters through conjugate addition a challenging task.[2] Nevertheless, due to the fundamental importance of this structural element, the development of enantioselective conjugate addition methods to access all-carbon quaternary stereocenters has gained increasing attention over the last years.[3,4]

In the course of our total synthesis of (±)-taiwaniaquinol B (**1**) (Scheme 1), our group noted the ease of formation of all-carbon benzylic quaternary centers through addition of MeMgBr to alkylidene Meldrum's acid **2** to form **3** in excellent yield under mild reaction conditions.[5] The construction of this structural motif through conjugate addition to 5-(1-arylalkylidene) Meldrum's acids was unknown. However, it had been obtained by 1,4-addition of aryl

(1) For reviews on conjugate addition, see: (a) Thaler, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 645–648. (b) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039–1075. (c) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852. (d) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823. (e) Alexakis, A.; Vuagnoux-d'Augustin, M.; Martin, D.; Kehrli, S.; Palais, L.; Hénon, H.; Hawner, C. *Chimia* **2008**, *62*, 461–464. (f) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969–5994. (g) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279–1300. (h) López, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179–188. (i) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; pp 224−258. (j) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236. (k) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196. (l) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061.

(2) For an overview on asymmetric synthesis of all-carbon quaternary carbon centers, see: (a) *Quaternary Stereocentres: Challenges and Solutions for Organic Synthesis*; Christophers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, 2006. (b) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396. (c) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473–1482. (d) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363–5367. (e) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105–10146. (f) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591–4597. (g) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401.

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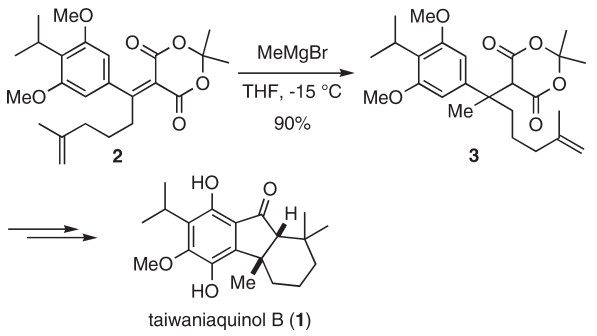
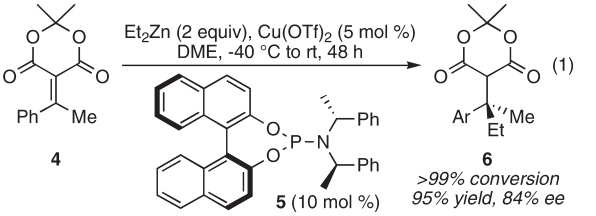
SCHEME 1. Formation of Benzylic All-Carbon Quaternary Center toward the Total Synthesis of Taiwaniaquinol B



Grignard and organocopper reagents to 5-(1-alkylalkylidene) Meldrum's acids.[6] At the outset of this project, asymmetric versions of either of these approaches were unprecedented.[7]

Meldrum's acid derivatives[8] are highly useful intermediates in a variety of chemical transformations, and alkylidene Meldrum's acids possess, from a practical viewpoint, a number of advantageous features: (a) olefin geometrical symmetry, which avoids difficult substrate preparation/separation of *Z*/*E* isomers, (b) general means of preparation by Knoevenagel condensation with a variety of ketones, and (c) their crystalline nature, which permits purification by crystallization/trituration.

Following the completion of the first total synthesis of taiwaniaquinol B (**1**), we embarked on developing an asymmetric version of the conjugate addition of organometallic reagents to 5-(1-arylalkylidene) Meldrum's acids. The copper-catalyzed conjugate addition of dialkylzinc reagents to alkylidene Meldrum's acids was initiated using 5-(1-phenylethylidene) derivative **4** to probe the reactivity of the diactivated tetrasubstituted olefin. Treating Meldrum's acid **4** with Et_2Zn in the presence of catalytic amounts of copper-(II) triflate and phosphoramidite ligand[9] **5** furnished desired product **6** in >99% conversion, 95% yield, and 84% enantiomeric excess (eq 1).[4d,10] This initial result illustrated the superior electrophilicity of alkylidene Meldrum's acids[11] and its value in the formation of all-carbon benzylic quaternary centers via enantioselective conjugate addition.



Herein, a systematic study outlining the enantioselective 1,4-addition of dialkylzinc reagents to 5-(1-arylalkylidene) and indenylidene Meldrum's acids is presented. Variation of the aryl and alkyl groups present on the alkylidene was explored thoroughly. The enantioselection was dependent on the pattern of substitution of the arene, with para-substituted aryl groups consistently leading to high enantioselectivities. The nature of the organozinc reagent on the efficiency and selectivity of the conjugate addition was also investigated. The solid-state conformation was determined for a number of alkylidene Meldrum's acids and correlated with the observed enantioselectivity in relation to the pattern of substitution of the arene moiety.

Results and Discussion

Influence of the Substrate Structural Elements on the Enantioselectivity of the Conjugate Addition. The scope of the enantioselective 1,4-addition was initially examined by studying the effect of the aromatic ring directly attached to the electrophilic carbon of the alkylidene (Table 1). The

(3) Alexakis' group: (a) Henon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., In. Ed.* **2008**, *47*, 9122–9124. (b) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8211–8214. (c) 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. (d) Vuagnoux-d'Augustin, M.; Kehrli, S.; Alexakis, A. *Synlett* **2007**, 2057–2060. (e) Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem.—Eur. J.* **2007**, *13*, 9647–9662. (f) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417. (g) Fuchs, N.; d'Augustin, M.; Humam, M.; Alexakis, A.; Taras, R.; Gladiali, S. *Tetrahedron: Asymmetry* **2005**, *16*, 3143–3146. (h) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376–1378. Hoveyda's group: (i) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358–7362. (j) Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12904–12906. (k) Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097–1100. (l) Lee, K.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184. (m) Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988–14989. (n) Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584–4585. Hayashi's group: (o) Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588–13589. (p) Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628–5629. Carretero's group: (q) Mauleón, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961–4963. Tomioka's group: (r) Matsumoto, Y.; Yamada, K.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578–4581.

(4) (a) Wilsily, A.; Lou, T.; Fillion, E. *Synthesis* **2009**, 2066–2072. (b) Wilsily, A.; Fillion, E. *Org. Lett.* **2008**, *10*, 2801–2804. (c) Fillion, E.; Wilsily, A.; Liao, E-T. *Tetrahedron: Asymmetry* **2006**, *17*, 2957–2959. (d) Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775.

(5) Fillion, E.; Fishlock, D. *J. Am. Chem. Soc.* **2005**, *127*, 13144–13145.

(6) For a recent example, see: (a) Limanto, J.; Shultz, C. S.; Dorner, B.; Desmond, R. A.; Devine, P. N.; Krska, S. W. *J. Org. Chem.* **2008**, *73*, 1639–1642. For all reports prior to our total synthesis, see: (b) Vogt, P. F.; Molino, B. F.; Robichaud, A. J. *Synth. Commun.* **2001**, *31*, 679–684. (c) Davis, A. P.; Egan, T. J.; Orchard, M. G. *Tetrahedron* **1992**, *48*, 8725–8738. (d) Fleming, I.; Moses, R. C.; Tercel, M.; Ziv, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 617–626. (e) Huang, X.; Chan, C.; Wu, Q. *Synth. React. Inorg. Met.-Org. Chem.* **1982**, *12*, 549–556. (f) Huang, X.; Chan, C.; Wu, Q. *Tetrahedron Lett.* **1982**, *23*, 75–76. For Michael addition of nitromethane for the formation of quaternary carbon, see: (g) Li, J.; Li, Z.; Chen, Q. *J. Chem. Res.* **2004**, 758–759. For the formation of 1,5-diionic phosphorous betaines, see: (h) Yavari, I.; Anary-Abbasinejad, M.; Alizadeh, A.; Habibi, A. *Phosphorus Sulfur Silicon* **2002**, *177*, 2523–2527.

(7) Asymmetric synthesis of tertiary carbon centers from alkylidene Meldrum's acids and dialkylzinc reagents: (a) Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682–9683. (b) Watanabe, T.; Knöpfel, T. F.; Carreira, E. M. *Org. Lett.* **2003**, *5*, 4557–4558.

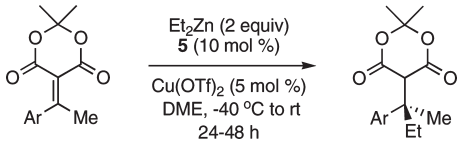
(8) For reviews on Meldrum's acid in synthesis, see: (a) Ivanov, A. S. *Chem. Soc. Rev.* **2008**, *37*, 789–811. (b) Chen, B.-C. *Heterocycles* **1991**, *32*, 529–597. (c) Strozhev, M. F.; Lielbriedis, I. É.; Neiland, O. Ya. *Khim. Geterotsikl. Soedin.* **1991**, 579–599. (d) McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345–358.

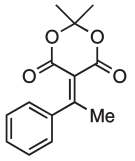
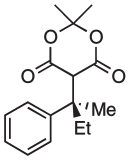
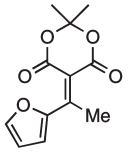
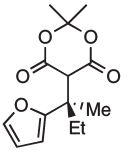
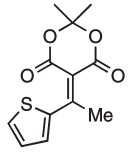
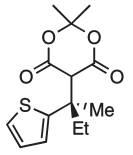
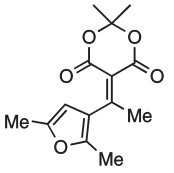
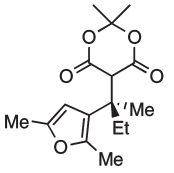
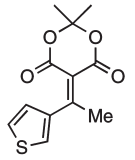
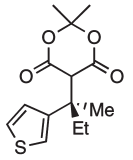
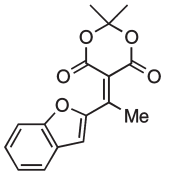
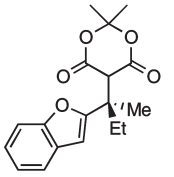
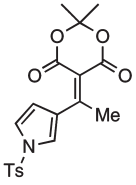
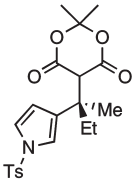
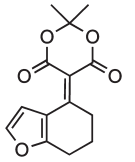
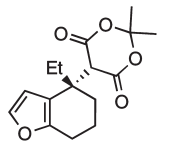
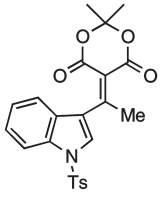
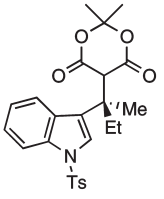
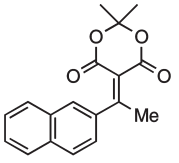
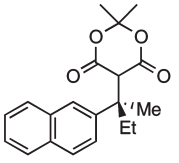
(9) (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353. (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620–2623. (c) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374–2376.

(10) The absolute stereochemistry of Meldrum's acid **6** was assigned by derivatization to known compounds; see ref 4d.

(11) An interesting observation was made regarding the overall superior electrophilicity of alkylidene Meldrum's acids compared to their structurally similar alkylidene dimethyl malonates. Under conditions in which alkylidene Meldrum's acid **4** is alkylated in >99% conversion, the analogous alkylidene malonate was inert. For asymmetric 1,4-addition of organozinc or aluminum reagents to alkylidene malonates for the formation of tertiary stereocentres, see: (a) Schppan, J.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 792–793. (b) Alexakis, A.; Benhaim, C. *Tetrahedron: Asymmetry* **2001**, *12*, 1151–1157.

TABLE 1. Enantioselective 1,4-Addition to Heteroaromatic-Substituted Alkylidene Meldrum's Acids



entry	substrate	product	yield (%)	ee (%)	entry	substrate	product	yield (%)	ee (%)
1[a]	 **4**	 **6**	95	84	6	 **15**	 **16**	97	91
2	 **7**	 **8**	77	92	7	 **17**	 **18**	92	84
3	 **9**	 **10**	95	96	8	 **19**	 **20**	63	77
4	 **11**	 **12**	99	96	9	 **21**	 **22**	77	76
5	 **13**	 **14**	74	96	10	 **23**	 **24**	66	95

[a]Average of two experiments for the isolated yield and ee.

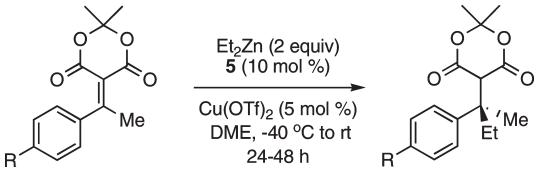
importance of heteroaromatic ring systems in medicinally relevant compounds inspired us to examine these types of arenes.

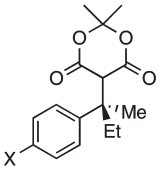
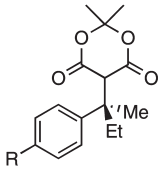
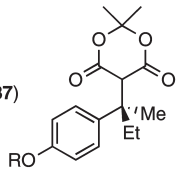
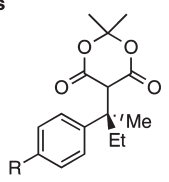
2-Thiophene- and 3-thiophene-substituted alkylidenes **7** and **9** furnished addition products **8** and **10** in 92 and 96% ee, respectively (Table 1, entries 2 and 3). Tosylated pyrrole and indole derivatives **11** and **13** gave excellent enantioselectivities and yields (Table 1, entries 4 and 5).[12] Furyl-substituted alkylidenes **15** and **17**, when subjected to the reaction conditions, provided products **16** and **18** in 91% and 84% ee, respectively (Table 1, entries 6 and 7). On the other hand, decreased enantioselectivities were observed for benzo- and fused furyl derivatives (Table 1, entries 8 and 9). Although 1-naphthyl-substituted alkylidene led to complete recovery of starting material, possibly due to steric hindrance of the electrophilic carbon center, 2-naphthyl-substituted alkylidene **23** furnished **24** in an excellent 95% ee (entry 10).

The variation in heteroatoms, steric hindrance, and electron richness or poorness of the heteroatomics presented in Table 1 prevented systematic comparison of the factors affecting the enantioselectivity of the conjugate addition. Therefore, additions to 1-arylalkylidene Meldrum's acids

(12) It was necessary that the nitrogen substituent be electron-withdrawing group to prevent decomposition of isolated products. Otherwise, elimination of the heteroaromatic ring generating 1-alkylalkylidenes Meldrum's acid was observed.

TABLE 2. Para-Substituted 5-(1-Arylalkylidene) Meldrum's Acids



entry	substrate	product		yield (%)	ee (%)	entry	substrate	product		yield (%)	ee (%)
Halogens						***sp*- and sp²-hybridized carbon substituents**					
1[a]	X = Cl (**25**)		**26**	88	95	11[a]	R = Ph (**45**)		**46**	76	95
2[a]	X = Br (**27**)		**28**	84	92	12	R = $CHCH_2$ (**47**)		**48**	90	94
3[a]	X = F (**29**)		**30**	83	92	13	R = CO_2Me (**49**)		**50**	99	93
4	X = CF_3 (**31**)		**32**	87	92	14	R = CCTIPS (**51**)		**52**	95	97
Phenol derivatives						**Inductively donating groups**					
5	R = Bn (**33**)		**34**	75	93	15	R = Me (**53**)		**54**	82	89
6	R = TIPS (**35**)		**36**	81	94	16	R = *i*-Pr (**55**)		**56**	88	98
7	R = TBDMS (**37**)		**38**	74	96	17[a]	R = *t*-Bu (**57**)		**58**	91	99
8	R = *i*-Pr (**39**)		**40**	84	95	18	R = TMS (**59**)		**60**	90	93
9	R = *t*-Bu (**41**)		**42**	87	95						
10	R = Ac (**43**)		**44**	87	93						

[a]Average of two experiments for the isolated yield and ee.

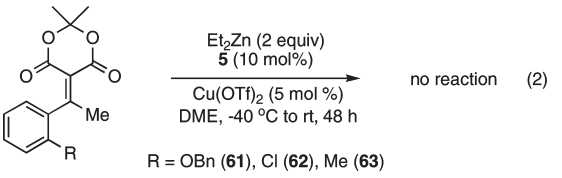
were investigated as this would provide control of both steric and electronic properties by varying the substituent and its position on the aromatic ring. We began our study with examination of substituent at the para position, with the expectation that conjugation to the electrophilic alkene would reveal a strong electronic effect, while remoteness from the site of the addition would make the steric contribution insignificant (Table 2).

Electron-withdrawing halogens and a trifluoromethyl group at the para position of the aromatic moiety, when subjected to the optimized reaction conditions using Et_2Zn, resulted in increased enantioselectivities when compared to alkylidene **4**, ranging from 92% to 95% (Table 2, entries 1−4). Similarly, phenol derivatives furnished products with enantiomeric excesses between 93% and 96% in good isolated yields (Table 2, entries 5−10). An array of phenol protecting groups such as benzyl, alkyl, and silyl ethers and acetyl esters were compatible with the mild reaction conditions.

Substituents bearing an sp^2-hybridized carbon directly attached to the aromatic moiety, including phenyl, vinyl, and ester groups, gave the addition products in excellent yields and up to 95% ee (Table 2, entries 11−13). Silyl-protected alkyne derivative **51** furnished the conjugate addition product **52** in 97% ee (Table 2, entry 14).

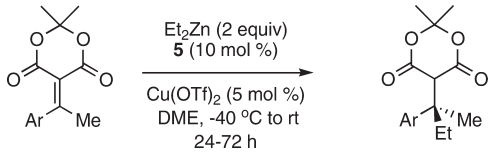
Inductively donating alkyl groups showed a significant increase in enantioselectivities with increasing size to yield products with up to 99% ee and 91% yield (Table 2, entries 15−17). The analogous but sterically less demanding trimethylsilyl group furnished the addition product in excellent enantioselectivity, although inferior to the *tert*-butyl group (Table 2, entry 18).

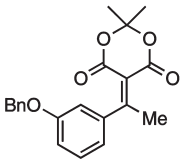
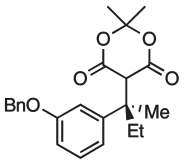
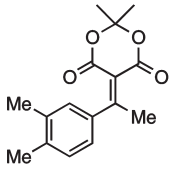
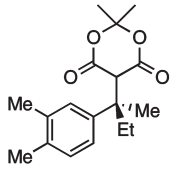
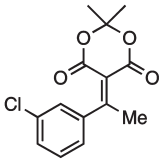
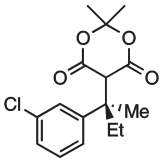
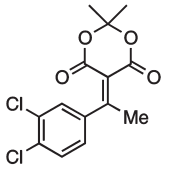
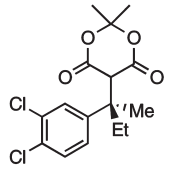
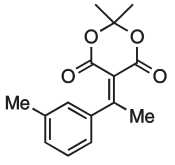
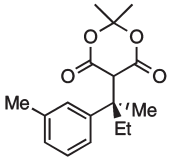
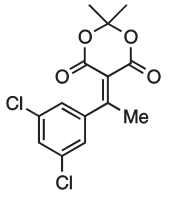
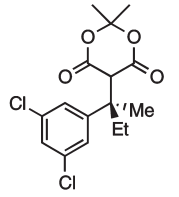
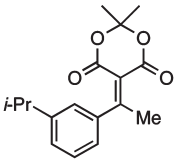
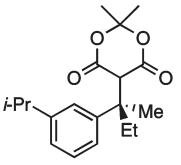
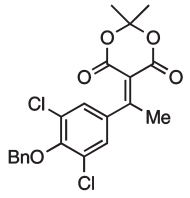
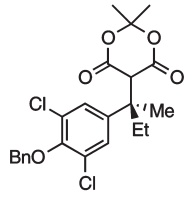
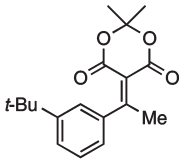
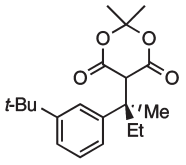
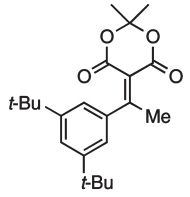
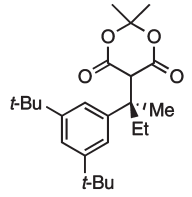
The influence of the aromatic moiety on the enantioselective copper-catalyzed 1,4-addition was further probed with ortho-substituted 1-arylalkylidene Meldrum's acid derivatives. Electron-donating benzyloxy group (**61**), electron-withdrawing chloro group (**62**), and σ-donating methyl (**63**) groups all had the same outcome; complete recovery of starting material after 48 h (eq 2). It is interesting to note that analogously substituted 2-methyl-3-furylalkylidene **17**, where the benzene ring has been replaced with a furan, gave Meldrum's acid **18** in 92% yield and 84% ee (Table 1, entry 7).



The effect of substituting the meta position of 1-arylalkylidene Meldrum's acids in the enantioselective conjugate addition reaction was then examined. While meta-substituted arylalkylidene Meldrum's acids did participate in the reaction, the enantioselectivites of the observed products were contrastingly and considerably lower than the ones obtained with the analogous para-substituted arylalkylidene Meldrum's acids. Benzyloxy, chloro, and methyl derivatives **64**, **66**, and **68** furnished products containing an all-carbon benzylic quaternary stereocenter in 74−79% ee (Table 3,

TABLE 3. Meta-Substituted 5-(1-Arylalkylidene) Meldrum's Acids



entry	substrate	product	yield (%)	ee (%)	entry	substrate	product	yield (%)	ee (%)
1[a]	 **64**	 **65**	97	79	6	 **74**	 **75**	98	91
2[a]	 **66**	 **67**	96	74	7	 **76**	 **77**	88	85
3[a]	 **68**	 **69**	93	78	8[b]	 **78**	 **79**	91	50
4	 **70**	 **71**	91	97	9[b]	 **80**	 **81**	82	59
5[a]	 **72**	 **73**	99	98	10[b]	 **82**	 **83**	31	26

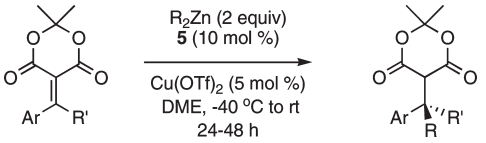
[a]Average of two experiments for the isolated yield and ee. [b]The catalyst loading and reaction time were increased: $Cu(OTf)_2$ (8 mol %), ligand **5** (16 mol %) for 72 h.

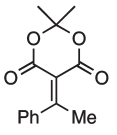
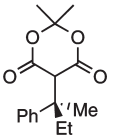
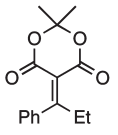
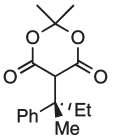
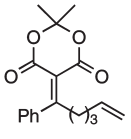
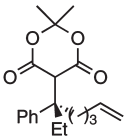
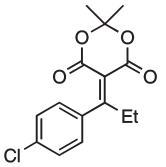
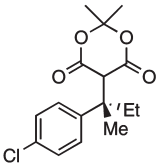
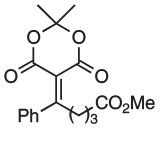
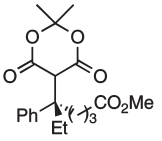
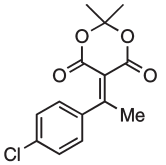
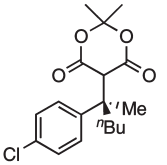
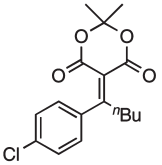
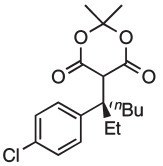
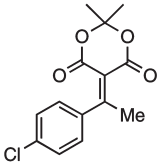
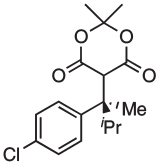
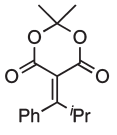
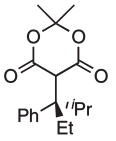
entries 1−3),[13] compared to 89−95% for the corresponding para substrates (Table 2, entries 1, 5, and 15). Conversely, *i*-Pr and *t*-Bu groups, which caused a substantial increase in ee's at the *para* position, led to identical results when located at the meta position, to provide, from alkylidenes **70** and **72**, Meldrum's acids **71** and **73** in 97% and 98% ee, respectively (Table 3, entries 4 and 5).

The combined influence of para and meta substituents on the enantioselectivity of the addition was also of interest. When 3,4-dimethylphenyl alkylidene Meldrum's acid **74** was subjected to the optimized conjugate addition conditions, **75** was obtained in 91% ee (Table 3, entry 6). For comparison, *p*-methyl derivative **53** gave **54** in 89% ee (Table 2, entry 15), while

(13) The absolute stereochemistry of **67** was assigned by X-ray crystallography; see the Supporting Information.

TABLE 4. Varying the Alkylidene Meldrum's Acids and Dialkylzinc Reagents



entry	substrate	product	R_2Zn	yield (%)	ee (%)	entry	substrate	product	R_2Zn	yield (%)	ee (%)
1	 **4**	 **6**	Et_2Zn	95	84	6[a]	 **92**	 *ent*-**6**	Me_2Zn	93	76
2	 **84**	 **85**	Et_2Zn	60	89	7[a]	 **93**	 *ent*-**26**	Me_2Zn	68	90
3	 **86**	 **87**	Et_2Zn	67	89	8[b]	 **25**	 **94**	$^nBu_2Zn$	87	87
4	 **88**	 **89**	Et_2Zn	78	94	9[b]	 **25**	 **95**	$^iPr_2Zn$	99	65
5	 **90**	 **91**	Et_2Zn	NR	N/A						

[a] Me_2Zn (2 equiv) was used with the 2-naphthyl derivative of ligand **5** (10 mol %). [b] Average of two experiments for the isolated yield and ee.

m-methyl compound **68** furnished **69** in 78% ee (Table 3, entry 3). A similar trend was observed with 3,4-dichlorophenyl alkylidene Meldrum's acid **76**, which led to **77** in 85% ee (Table 3, entry 7). Monosubstituted 3-chlorophenyl and 4-chlorophenylalkylidene Meldrum's acids **66** and **25** furnished 1,4-addition products **67** and **26** in 74% and 95% ee, respectively.

On the other hand, substituting the two meta positions was adversely additive, and 3,5-dichloro derivative **78** yielded **79** in a modest 50% ee (Table 3, entry 8). A similar result was obtained with alkylidene **80** (Table 3, entry 9). When both meta positions were substituted, a decrease in the level of conversion was also noted. For the reactions to proceed to completion, higher catalyst loadings and prolonged reaction times were required (entries 8−10). The negative impact of substituting both meta positions was further illustrated with alkylidene **82**, which gave Meldrum's acid **83** in a low 26% ee and 31% yield.[14] In contrast, an exceptionally high enantiomeric excess of 98% was obtained with mono-*tert*-butyl-substituted **72**.

The reactions discussed above described the addition of Et_2Zn to 5-(1-arylalkylidene) Meldrum's acids as an entry into ethyl, methyl-substituted all-carbon benzylic stereocenters. The nature of the alkyl substituents present on the all-carbon stereocenter was broadened by either varying the alkyl substituent on the alkylidene moiety or the diorganozinc reagent. As depicted in Table 4, linear alkyl chains gave slightly superior enantioselectivities in the conjugate

(14) Despite higher catalysts loading, a low 59% conversion was observed.

addition (entries 2−4) when compared to ethylidene **4**. It is important to note that terminal alkene and methyl ester were compatible with the mild reaction conditions. In contrast, alkyl chains branched at the 2-position of the alkylidene hampered the addition, as illustrated with isopropyl derivative **90** (entry 5).[15]

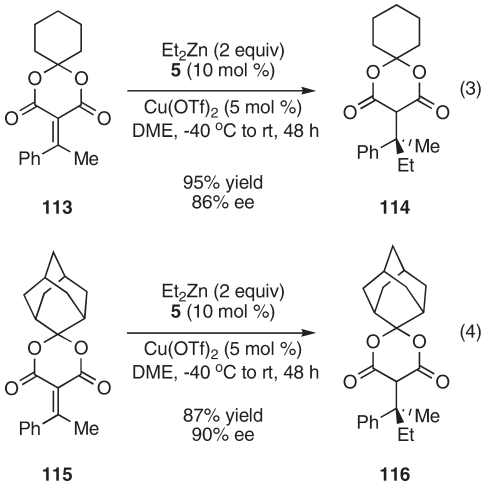
Alternatively, the alkyl groups on the all-carbon benzylic quaternary carbon center were varied by the addition of dialkylzinc reagents other than Et_2Zn. The enantiomers of addition products **6** and **26**, formed by addition of Et_2Zn to **4** and **25** (Table 4, entry 1 and Table 2, entry 1), were synthesized by the addition of Me_2Zn to **92** and **93** in 76% and 90% ee, respectively. Our efforts to overcome the poor reactivity of alkylidene Meldrum's acids toward the addition of Me_2Zn, and the associated low level of conversion, were recently reported.[4a] These issues were successfully addressed by conducting the conjugate addition at higher concentration with 2-fold excess of Me_2Zn.[16] Under these optimized conditions, the addition of Me_2Zn gave *ent*-**6** and *ent*-**26** in good isolated yields (Table 4, entries 6 and 7). Furthermore, the addition of *n*-Bu_2Zn proceeded smoothly to give **94** in 87% ee (Table 4, entry 8). On the other hand, addition of *i*-Pr_2Zn gave a high yield but afforded product **95** in lower ee than with other nucleophiles (Table 4, entry 9). However, this was the only mean of accessing sterically hindered quaternary centers with α-branched substituents, as alkylidene Meldrum's acid **90** was unreactive (Table 4, entry 5 vs 9).

Next, the reactivity of conformationally constrained indenylidene Meldrum's acids, obtained via Knoevanagel condensation of 1-indanones with Meldrum's acid, was explored (Table 5). Subjecting indenylidene Meldrum's acid **96** to the optimized reaction conditions furnished indan[17] **97** in 96% ee, a substantial increase in enantioselectivity from analogous 1-phenylethylidene **4**, which yielded Meldrum's acid **6** in 84% ee (Table 5, entry 1, vs eq 1). Furthermore, as observed previously with nonfused alkylidene Meldrum's acids, substitution at the para position on the aromatic moiety relative to the electrophilic center enhanced the enantioselection (Table 5, entry 2). Dialkylzinc reagents Me_2Zn and *n*-Bu_2Zn reacted effectively with **98**, yielding **100** and **101** in 99% and 97% ee, respectively (Table 5, entries 3 and 4). Similar to the addition of *i*-Pr_2Zn to alkylidene **25** (Table 4, entry 9), low enantiomeric excess was obtained with indenylidene **98** (Table 5, entry 5).

Indenylidene Meldrum's acids possess two different meta positions relative to the electrophilic carbon center. The respective influence of the meta positions on the enantioselectivity of the conjugate addition was then investigated by preparing a series of indenylidene Meldrum's acids substituted with groups of various electronic properties. Chloro-substituted indenylidene Meldrum's acid **103** provided indan **104** in an exceptionally high >99% ee, while analogous Meldrum's acid **105** yielded indan **106** in a modest 79% ee (Table 5, entries 6 and 7).[18] Dichloro-substituted indenylidene Meldrum's acid **107** furnished **108** in excellent yield and enantiomeric excess (Table 5, entry 8), which is in contrast with the low selectivity obtained with dichlorophenylalkylidene **78** (Table 3, entry 8).

An identical trend was observed with regioisomeric indenylidene Meldrum's acids **109** and **111**, substituted with a methoxy group (Table 5, entries 9 and 10). This series of alkylidenes revealed that high enantioselectivities were observed when the 6-position of the indenylidene Meldrum's acid was substituted, while substituting the 4-position substantially decreased the ee's to the midseventies range, regardless of the electronic nature of the group.

A last variant to explore on defining the factors influencing the enantioselectivity of the conjugate addition onto alkylidene Meldrum's acid electrophiles was to use cyclic malonates derived from the condensation of malonic acid with ketones other than acetone. It was found that alkylidenes derived from cyclohexanone (**113**) and adamantone (**115**) provided yields and ee's similar to standard Meldrum's acid (eqs 3 and 4). Although adamantyl derivative **115** did provide a slight improvement in ee over alkylidene **4**, this gain did not justify the use of a more expensive and noncommercially available starting material.



Rationalizing the Influence of the Substrate Structural Elements on the Enantioselectivity of the Conjugate Addition. In a recent review on enantioselective copper-catalyzed conjugate addition, Alexakis and co-workers presented a tentative catalytic cycle for the addition of dialkylzinc reagents to electron-deficient alkenes.[19] The authors proposed the formation of a $[CuL_2(alkyl)]\cdot$olefin π-complex as the enantiodetermining step in the conjugate addition. However, the complexity of the mechanism and the fact that several species are in equilibrium in solution[20] render the stereoregulating step of this complex pathway difficult to ascertain. Moreover, no three-dimensional model was advanced to

(15) The analogous cyclohexyl derivative was also unreactive toward conjugate addition of Et_2Zn.

(16) For the addition of Me_2Zn, the 2-naphthyl derivative of ligand **5** was used.

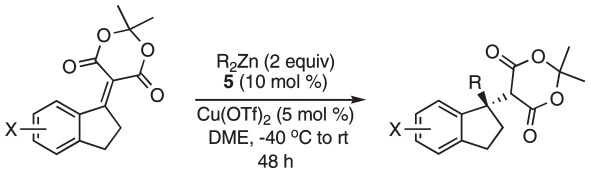
(17) Catalytic asymmetric synthesis of 1,1-disubstituted indanes: (a) García-Fortanet, J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 8108–8111. Catalytic asymmetric synthesis of 1-substituted indans: (b) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483. (c) Troutman, M. V.; Apella, D. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4916–4917. For reviews on the synthesis of indans, see: (d) Ferraz, H. M. C.; Aguilar, A. M.; Silva, L. F., Jr; Craveiro, M. V. *Quim. Nova* **2005**, *28*, 703–712. (e) Hong, B.; Sarshar, S. *Org. Prep. Proc. Int.* **1999**, *31*, 1–86.

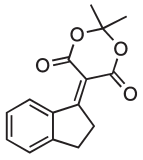
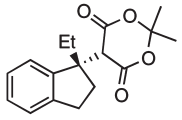
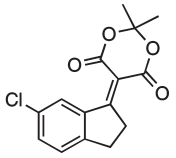
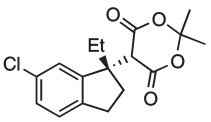
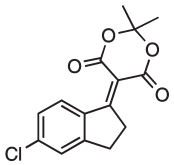
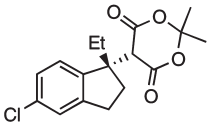
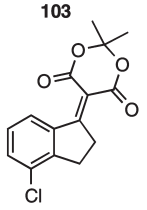
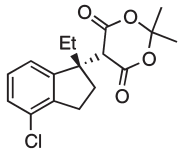
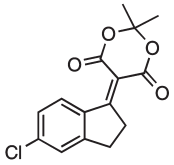
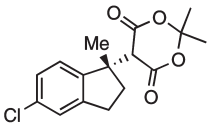
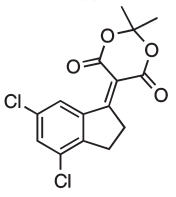
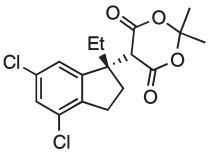
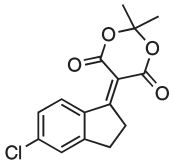
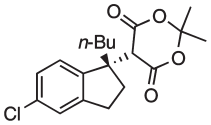
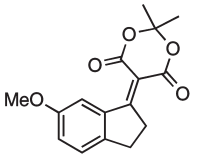
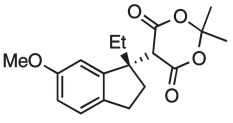
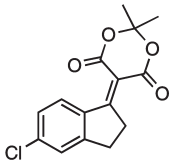
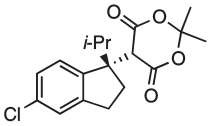
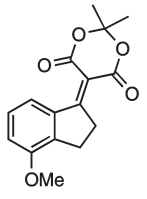
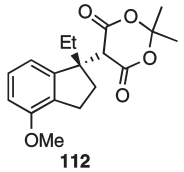
(18) The absolute stereochemistry of **106** was assigned by X-ray crystallography; see the Supporting Information.

(19) See page 2809 in ref 1d.

(20) Zhang, H.; Gschwind, R. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6391–6394.

TABLE 5. Enantioselective Conjugate Addition to Indenylidene Meldrum's Acids



entry	substrate	product	yield (%)	ee (%)	entry	substrate	product	yield (%)	ee (%)
1	 **96**	 **97**	96	96	6	 **103**	 **104**	87	>99
2[a]	 **98**	 **99**	94	99	7[a]	 **105**	 **106**	99	79
3[a,b]	 **98**	 **100**	98	99	8	 **107**	 **108**	86	97
4[a]	 **98**	 **101**	97	97	9[a]	 **109**	 **110**	99	99
5[a]	 **98**	 **102**	99	57	10	 **111**	 **112**	91	75

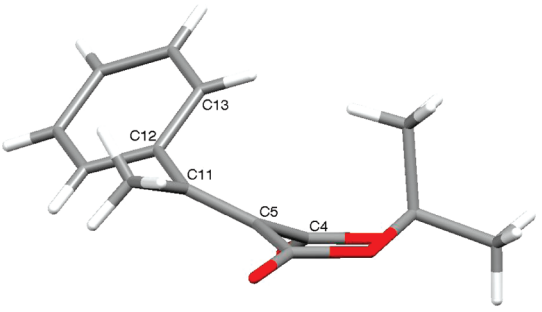
[b]Average of two experiments for the isolated yield and ee. [b]Me_2Zn (5 equiv) was used.

rationalize stereoinduction in enantioselective 1,4-addition using phosphoramidite ligands. We then applied Alexakis' premise to arylalkylidene Meldrum's acids, namely the formation of a $[CuL_2(alkyl)]\cdot$olefin complex as the enantiodetermining step, in an attempt to rationalize the observed variations in enantioselectivity in relation to the pattern of substitution of the aromatic moiety.

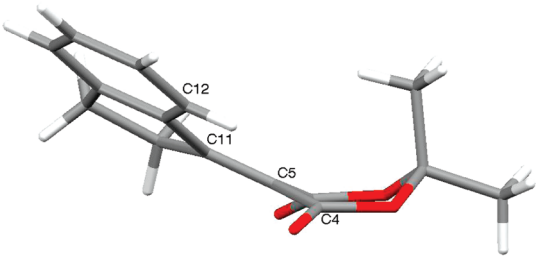
In the previous section, it was determined that, although ortho substitution was detrimental to the reaction, substituting the para or meta position of the aromatic moiety led to excellent conversions and yields of the desired products regardless of the electronic nature of the substituent, with the former consistently leading to high enantioselectivities. Sterically demanding *i*-Pr and *t*-Bu, when positioned at the para or meta position as depicted with substrates **55**, **57**, **70**, and **72**, provided optimal selectivities (Table 2, entries 16 and 17, and Table 3, entries 4 and 5). Additionally, conformationally restricted indenylidene Meldrum's acids furnished superior

enantiomeric excesses when compared to analogous 1-arylalkylidene Meldrum's acids (Table 5). Similarly, the presence of a substituent on the aromatic moiety para (5-position) to the electrophilic carbon center was beneficial and resulted in higher enantioselection (Table 5, entry 1 vs 2). Additional information on the spatial arrangement of the meta group relative to the electrophilic olefin and its effect on the enantioselectivity of the 1,4-addition was obtained; substituting the 4-position furnished modest ee's while substitution of the 6-position had a drastically opposite effect, leading to high ee's (Table 5, entries 6 and 9 versus entries 7 and 10). The absolute configuration of compounds **6**, **67**, and **106** was determined by derivatization or X-ray crystallography, and the sense of induction was identical in all cases, suggesting a similar enantiodetermining step.

The observations with 1-arylalkylidene and indenylidene Meldrum's acids presented above were opposite to our initial postulate, expecting that conjugation of the arene with the electrophilic alkene would reveal a strong electronic effect, especially for the para- and meta-substituted substrates, while remoteness from the site of the addition would make the steric contribution insignificant. The enhanced results obtained with the indenylidene derivatives suggest that the conformation adopted by the planar bicyclic system led to optimal interaction with the chiral copper species in the enantiodetermining step for electronic and/or steric reasons. Since experimental data suggested that the enantiodetermining step was strongly affected by steric factors, we then attempted to draw a parallel between the conformation adopted by the indenylidene Meldrum's acids and the 1-arylalkylidene Meldrum's acids in the course of the conjugate nucleophilic addition by obtaining the X-ray structures of Meldrum's acids **4** and **96**. A conformational similarity was revealed; in both compounds, the Meldrum's acid moiety was in a boat conformation (Figure 1).[21] The phenyl ring and the olefin in **4** were out-of-plane, with a dihedral angle C(5)−C(11)−C(12)−C(13) of −56.7°. On the contrary, indenylidene **96** displayed a planar arrangement of the aromatic moiety with the alkene, suggesting conjugation. Examination of the *cis*-substituents around the olefin acceptor showed an out-of-plane arrangement of these groups. For alkylidene **4**, the dihedral angle C(4)−C(5)−C(11)−C(12) was −10.8°, compared to a substantially more pronounced C(4)−C(5)−C(11)−C(12) of 15.4° for indenylidene **96**. Also, a significant C=C bond length difference was noted; 1.34 Å for **4** versus 1.37 Å for **96**. The elongated C=C bond may explain the superior electrophilicity of the indenylidene systems. Furthermore, during the formation of the sp^3-hybridized all-carbon quaternary center from the sp^2-hybridized electrophilic carbon, the aromatic group in conjugation with the olefin might play a role in facilitating the conjugate addition by stabilizing the transition state.



Alkylidene Meldrum's acid ***4***



Indenylidene Meldrum's acid ***96***

FIGURE 1. X-ray structures of 5-(1-phenylethylidene) Meldrum acid (**4**) and 5-(2,3-dihydro-1*H*-1-indenylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**96**).

The effect of substituting the para position of the arene on the conformation of alkylidene and indenylidene Meldrum's acids in the solid state was then studied by elucidating the X-ray structures of compounds **25**, **57**, and **98**. The conformation of 5-[1-(4-chlorophenyl)ethylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**25**) and 5-(1-(4-*tert*-butylphenyl)-ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**57**) was comparable to **4**, with a boat conformation for the Meldrum's acid moiety and the aromatic and olefin being out-of-plane. The 4-chlorophenyl ring and the alkene in **25** were almost perpendicular with a dihedral angle C(5)−C(11)−C(12)−C(13) of −84.8°. Like **96**, analogous chloroindenylidene **98** was planar, with the aromatic ring in conjugation with the olefin. An elongated C=C bond of 1.36 Å was observed for **98**, compared to 1.34 Å for **25**. When comparing **25** and **57**, their conformations were practically indistinguishable. Compound **57** displayed a dihedral angle C(5)−C(11)−C(12)−C(17) of 99.2° and a C=C bond length of 1.35 Å.[22]

Despite the conformational discrepancies observed between alkylidene Meldrum's acids **25** and **57** and indenylidene Meldrum's acid **96** and **98**, comparable enantiomeric excesses and identical sense of induction were obtained with both systems. On the other hand, although displaying identical conformations, a difference of 11−15% in enantiomeric excess was noted when comparing Meldrum's acids **4** to **25** and **57**. This series of results seems to indicate that the

(21) This is consistent with published crystallographic data for alkylidene Meldrum's acids. (a) For a recent discussion on Meldrum's acid's boat conformation, see: Chopra, D.; Zhurov, V. V.; Zhurova, E. A.; Pinkerton, A. A. *J. Org. Chem.* **2009**, *74*, 2389–2395. (b) For the crystal structure of 5-(benzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (monosubstituted alkylidene), see: Dong, N.; Cai, G.-Q.; Wu, N.-C.; Huang, X.; Hu, S.-Z.; Chen, M.-D.; Mak, T. C. W *Chin. Sci. Bull.* **1989**, *34*, 1955–1960. (c) For a review on the conformation of alkylidene Meldrum's acids and similar derivatives, see: Sato, M.; Sunami, S.; Kaneko, C. *Heterocycles* **1996**, *42*, 861–883. (d) For a discussion of benzyl Meldrum's acid conformation, see: Shengzhi, H. *J. Struct. Chem.* **1985**, *4*, 107–114. (e) Original structure determination by X-ray crystallography: Pfluger, C. E.; Boyle, P. D. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1547–1549.

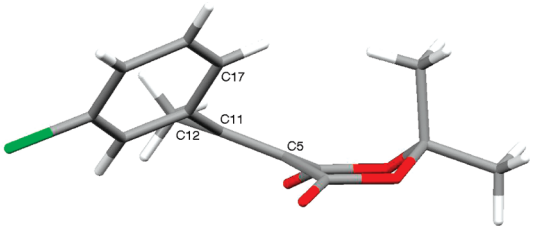
(22) The unit cell contains two molecules, thus two sets of data. The dihedral angle C(27)−C(33)−C(34)−C(39) for the second molecule is −100.4°. Bond length C(27)−C(33) is 1.35 Å.

solid-state conformation of 1-arylakylidene Meldrum's acids alone is not reflective of the enantiodetermining step. Accordingly, the conformation adopted by the $[CuL_2(alkyl)]\cdot$ alkene complex is likely similar to the one determined in the solid state for constrained indenylidene Meldrum's acids. That key conformation is attained by the 1-arylakylidene Meldrum's acids through rotation of the C−C σ-bond linking the aromatic moiety to the electrophilic carbon center. As judged by the identical sense and level of induction, the introduction of a substituent at the para position of the arene offers a superior control in the enantiodetermining step by the catalyst through steric interactions between the substrate's remote substituents and the ligands present on the Cu center.

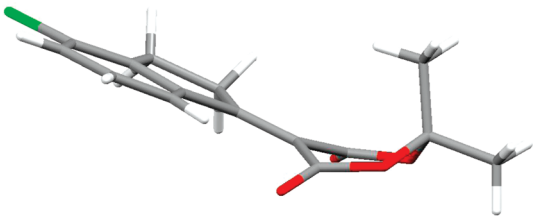
As depicted in eq 2, 1-arylalkylidenes bearing a substituent at the ortho position were subjected to the optimized 1,4-conjugate addition reaction conditions but resulted in recovery of starting material, regardless of the electronic nature of the substituent. At room temperature, the ^{1}H NMR spectrum of 2-benzyloxyphenylethylidene Meldrum's acid **61**, 2-chlorophenylethylidene Meldrum's acid **62**, and 2-methylphenylethylidene Meldrum's acid **63** exhibited two well-separated singlets, corresponding to the methyl groups on the Meldrum's acid moiety. The observation of diastereotopic methyl groups for the Meldrum's acid moiety suggested that these molecules displayed hindered rotation about the arylalkene C−C bond and exists as racemic atropoisomers.[23] X-ray analysis of alkylidene **62** and 2-methoxyphenylethylidene Meldrum's acid **117** (analogous to **61**) revealed identical three-dimensional structures, with a boat conformation for the Meldrum's acid moiety in both cases, and absence of conjugation of the aryl moiety with the olefin acceptor. In addition, the conformation adopted by compounds **62** and **117** placed the ortho substituent endo to the cup-shaped structure. The lack of reactivity for these alkylidenes was rationalized by the close proximity of the aromatic substituent to the olefin electrophilic carbon, hampering the formation of the catalyst·olefin complex, or simply blocking the delivery of the alkyl group.

Substituents such as methyl, benzyloxy, or chloro at the position meta to the electrophilic center were shown to have detrimental effects on the enantioselectivity (Table 3). Exceptionally high enantioselectivites were observed, however, when the meta position was substituted with large *i*-Pr and *t*-Bu groups. To gain further insight on rationalizing the enantioselectivity observed for meta-substituted alkylidenes and indenylidenes, crystallographic data for **66**, **68**, **72**, **76**, **78**, **103**, and **105** were obtained.

5-[1-(3-Chlorophenyl)ethylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**66**) and 2,2-dimethyl-5-[1-(3-methylphenyl)-ethylidene]-1,3-dioxane-4,6-dione (**68**) showed identical conformations with the Meldrum's acid moiety in a boat conformation and a dihedral angle C(5)−C(11)−C(12)-C(17) of 57.6° for **66** (Figure 2) and 57.8° for **68**. Interestingly, compounds **66** and **68,** which gave similar enantioselectivity in the conjugate addition reaction, also showed a similar exo conformation of the meta substituent relative to the boat, meaning that the substituent points away from the cup-shaped structure. Comparison was made with



Alkylidene Meldrum's acid ***66***



Indenylidene Meldrum's acid ***105***

FIGURE 2. X-ray structures of 5-[1-(3-chlorophenyl)ethylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**66**) and 5-(4-chloro-2,3-dihydro-1*H*-inden-1-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**105**).

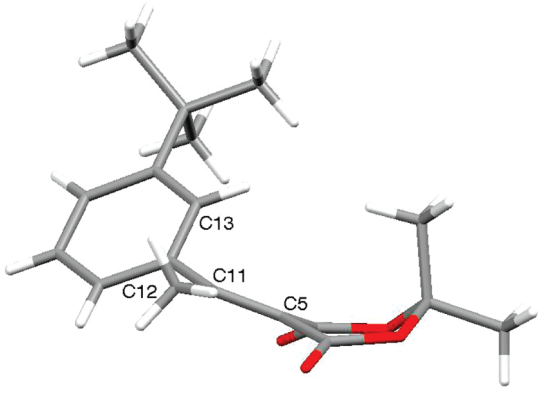
indenylidene Meldrum's acid **105**, which led to modest enantioselection in the conjugate addition, similar to **66** and **68**. As a working hypothesis, we postulated that the least nuclear motion principle[24] may be at play in the nucleophilic attack of alkylidene **66**. In the course of the enantiodetermining π-complex formation between the copper catalyst and olefin **66**, rotation of the aromatic ring would lead to a conformation similar to 4-substituted indenylidene Meldrum's acid **105** (Figure 2), which also led to modest enantioselection.[25] It is of note that low-temperature ^{1}H NMR studies could not detect the presence of atropoisomers for 3-substituted arylalkylidene Meldrum's acids. Therefore, when the meta substituent is pointing away from the cup-shaped structure of the alkylidene and indenylidene Meldrum's acids, the very large nucleophilic $CuL_2(alkyl)$ complex coordinates with the olefin with low discrimination for the enantiotopic faces, resulting in modest enantiomeric excesses.

In contrast, 5-(1-(3-*tert*-butylphenyl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**72**), which yielded the quaternary benzylic stereocenter in excellent enantioselectivity, displayed an endo conformation relative to the cup-shaped structure with a dihedral angle C(5)−C(11)−C(12)−C(13) of −55.6° (Figure 3). Again, using the least nuclear motion principle as a working hypothesis, in the course of the nucleophilic attack, the *tert*-butyl group would end up at the same spatial position as the 6-position of indenylidene Meldrum's acid following rotation of the aromatic ring,

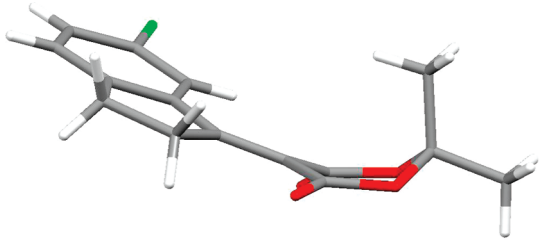
(23) An example of atropoisomerism with alkylidene Meldrum's acid was reported; see: Huck, N. P. M.; Meetsma, A.; Zijlstra, R.; Feringa, B. L. *Tetrahedron Lett*. **1995**, *36*, 9381–9384.

(24) (a) Sinnott, M. L. *Adv. Phys. Org. Chem*. **1988**, *24*, 113–204. (b) Hine, J. *Adv. Phys. Org. Chem*. **1977**, *15*, 1–61.

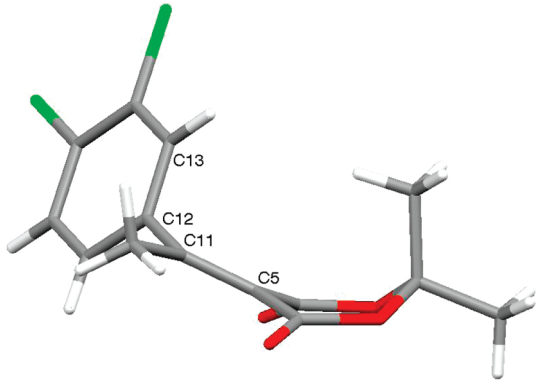
(25) 4-Chloro-substituted indenylidene diplayed a much lower dihedral angle than all the X-ray structures in this series, due to the presence of a C−H···O bond (2.16 Å) between one of the carbonyl group carbonyl group and a Csp^2−H (7-position). A persistent, intramolecular C−H···X (X = O, S, Br, Cl, and F) hydrogen bond in solution and solid states was previously reported for benzyl Meldrum's acid derivatives; see: Fillion, E.; Wilsily, A.; Fishlock, D. *J. Org. Chem*. **2009**, *74*, 1259–1267.



Alkylidene Meldrum's acid ***72***



Indenylidene Meldrum's acid ***103***



Alkylidene Meldrum's acid ***76***

FIGURE 3. X-ray structures of 5-(1-(3-*tert*-butylphenyl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**72**), 5-[1-(3,4-dichlorophenyl)ethylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**76**), and 5-(6-chloro-2,3-dihydro-1*H*-inden-1-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**103**).

leading to a conformation similar to Meldrum's acid **103** (Figure 3), for which superior enantioselection was observed. The correlation between solid-state conformation and enantioselection also applied to 5-[1-(3,4-dichlorophenyl)-ethylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**76**). A dihedral angle C(5)−C(11)−C(12)−C(13) of −81.8° was measured with a C═C bond length of 1.34 Å (Figure 3). The endo conformation was observed for Meldrum's acid **76**, and accordingly, conjugate addition yielded a good enantiomeric excess of 85% (Table 3, entry 7).

The experimental data seem to indicate that the spatial orientations of the meta substituents versus the cup-shaped structure of alkylidene Meldrum's acid influence the enantiodetermining step of the 1,4-addition. That is, an exo-disposed group is detrimental to enantioselection while an endo-oriented group is beneficial. This was further validated by the reaction of Et_2Zn with 3,5-disubstituted arylalkylidene Meldrum's acids **78**, **80**, and **82**, in which the exo and endo positions are filled, considering the rotation of the aromatic ring during the carbon−carbon bond-forming events. Not surprisingly, the products formed in low conversions and ee's (Table 3, entries 8−10) as important steric interactions develop between the chiral complex and the substrate in the formation of the π-complex. The exception is the reaction of 5-(4,6-dichloro-2,3-dihydro-1*H*-inden-1-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**107**), which furnished conjugate addition product **108** in high enantioselectivity (Table 5, entry 8). This is in striking contrast with the reactivity of analogous dichloro compound **78**. These results illustrates once again that the locked conformation adopted by the planar bicyclic system is most favorable in affecting reactivity and enantioselection.

In this section, evidence of a correlation between solid-state conformation and enantioselection in solution have been presented. However, to develop a reliable mnemonic device for predicting the level of stereoselectivity in the enantioselective conjugate addition reaction, the role of packing effects in the solid-state conformation observed for alkylidene and indenylidene Medrum's acids remained to be established, specially for meta-substituted 1-arylalkylidene Meldrum's acids. Nevertheless, from a practical point of view, the predictable increase in enantioselectivity by introduction of large substituents on the arene moiety provides a simpler means of producing highly enantioenriched products.

Summary

The scope and limitation of the asymmetric synthesis of all-carbon benzylic quaternary stereocenters via copper-catalyzed conjugate addition of primary dialkylzinc reagents to alkylidene and indenylidene Meldrum's acids has been studied. The reaction is tolerant to a wide range of heteroaromatic and functional groups. The significance of substituting the positions para, meta, and ortho to the electrophilic center was also highlighted. Substituting the ortho position leads to recovery of conjugate addition precursor, while substituting the para position leads to increased enantioselectivities. Small substituents at the meta position yield lower ee while large groups provide a substantial increase in facial selectivity. Steric interactions rather than electronic factors related to the substitutents on the aryl group likely cause the observed reactivity and enantioselectivity in the conjugate addition of organozinc reagents to alkylidene Meldrum's acids. A correlation between the observed enantioselectivity and the alkylidene Meldrum's acids solid-state conformation, determined by the arene pattern of substitution, was proposed.

Experimental Section

Preparation of Alkylidene Meldrum's Acids: General Procedure A. Alkylidene Meldrum's acids were prepared by the

Knoevenagel condensation of Meldrum's acid with ketones using Brown and co-workers' method.[26] In a typical reaction, a solution of $TiCl_4$ (2.1 equiv) in CH_2Cl_2 (3 M relative to ketone) was added dropwise under nitrogen to dry THF (0.3 M relative to ketone), which was cooled at 0 °C, resulting in a yellow suspension. A solution containing the ketone (1.0 equiv) and Meldrum's acid (1.0 equiv) in dry THF (0.7 M relative to ketone) was added dropwise via a syringe to the $TiCl_4 \cdot THF$ complex. The flask containing the solution of ketone and Meldrum's acid was rinsed with THF (2×) and added to the reaction mixture. Subsequently, pyridine (5.0 equiv) was added to the reaction mixture dropwise at 0 °C. The reaction was allowed to warm to room temperature slowly and stirred until completion of the reaction or for 24 h. The reaction was quenched by the addition of water and diluted with either Et_2O or EtOAc. After the solid was dissolved, the layers were partitioned. The aqueous layer was extracted with Et_2O or EtOAc (2×), and the combined organic layers were washed with a saturated solution of $NaHCO_3$ (2×) and brine (1×), dried over $MgSO_4$, filtered, and concentrated. Purification by either crystallization/trituration and/or flash chromatography provided the alkylidene Meldrum's acids.

4-(1-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)ethyl)phenyl Acetate (43). Prepared according to general procedure A. Recrystallization from MeOH afforded a light yellow solid in 68% yield: mp 144−145 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 2.68 (s, 3H), 2.27 (s, 3H), 1.79 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.0, 168.9, 161.0, 160.2, 151.3, 138.8, 127.3, 121.6, 116.9, 103.8, 27.2, 26.2, 21.1; HRMS(EI) m/z calcd for $C_{16}H_{16}O_6$ (M^+) 304.0947, found 304.0943.

1,4-Addition of (Alkyl)$_2$Zn to Alkylidene Meldrum's Acids: General Procedure B. Reactions were typically carried out using 0.12 mmol of substrate. In a glovebox, copper source (5 mol %) and phosphoramidite chiral ligand (10 mol %) were charged in a flame-dried resealable Schlenk tube. DME (0.5 mL) was then added to the Schlenk tube to wash down any residual solids to the bottom. The reaction mixture was allowed to stir at ambient temperature for 30 min, outside the glovebox, and then cooled to −40 °C. In the drybox, (alkyl)$_2$Zn solution (2.0 equiv) was transferred to a flask equipped with a septum. This solution was added to the Schlenk tube dropwise via a syringe, and the resulting solution was stirred for 5 min. A solution of alkylidene Meldrum's acid (1.0 equiv) in DME (0.5 mL) was then added dropwise via a syringe. Finally, DME (0.2 mL) was added to wash down the remaining solid on the sides of the Schlenk tube. The reaction mixture was allowed to warm slowly to room temperature. After being stirred for 48 h, the reaction mixture was cooled to 0 °C, and 5% HCl and EtOAc were added to the reaction mixture. The layers were partitioned, and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash column chromatography on silica gel using hexanes in EtOAc to yield the desired product. HPLC using a chiral column (OD-H or AD-H) was used to measure the enantiomeric ratio of the products.

(*R*)-4-(2-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)butan-2-yl)-phenyl Acetate (44). Compound **44** was prepared according to general procedure B with a reaction time of 29 h. Purification by flash column chromatography on silica gel, eluting with 3:1 hexanes/EtOAc, afforded a white, waxy solid in 87% yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 8.7 Hz, 2H), 3.54 (s, 1H), 2.26 (s, 3H), 2.15 (dq, J = 15.0, 7.3 Hz, 1H), 2.10 (dq, J = 14.4, 7.2 Hz, 1H), 1.61 (s, 3H), 1.58 (s, 3H), 1.19 (s, 3H), 0.78 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 164.5, 164.1, 149.6, 139.6, 128.0, 121.4, 105.4, 57.1, 46.0, 32.6, 29.5, 27.1, 22.2, 21.1, 8.7; enantiomeric excess of 93% (*R*) measured by chiral HPLC (AD-H, 5% *i*-PrOH/hexanes, 1.0 mL/min, t_{R1} = 13.2 min (*S*), t_{R2} = 14.1 min (*R*)); $[\alpha]^{26.5}_D$ = +5.9 (*c* 1.7, THF); absolute configuration was assigned by analogy to **6**, **67**, and **106**; HRMS(EI) m/z calcd for $C_{18}H_{22}O_6$ (M^+) 334.1416, found 334.1414.

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Supporting Information Available: Experimental procedures, NMR spectra, crytsallographic data, and CIF files for **4**, **25**, **57**, **62**, **66**, **67**, **68**, **72**, **76**, **78**, **96**, **98**, **103**, **105**, **106**, and **117**. This material is available free of charge via the Internet at http://pubs.acs.org.

(26) Baxter, G. J.; Brown, R. F. C. *Aust. J. Chem.* **1975**, *28*, 1551–1557.