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Tetrahedron: *Asymmetry* 17 (2006) 2957–2959

Tetrahedron: *Asymmetry*

# Asymmetric Cu-catalyzed 1,6-conjugate addition of dialkylzinc reagents to 5-(3-aryl-2-propenylidene) Meldrum's acids

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Received 20 October 2006; accepted 8 November 2006
Available online 28 November 2006

**Abstract**—The asymmetric synthesis of tertiary and quaternary stereocentres has been successfully achieved through Cu-catalyzed 1,6-addition of dialkylzinc reagents to 5-(3-aryl-2-propenylidene) Meldrum's acid derivatives in the presence of a phosphoramidite ligand.

## 1. Introduction

The conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyls is a powerful carbon–carbon bond forming process, and catalytic asymmetric versions have become useful synthetic tools for the generation of tertiary[1] and quaternary[2,3] carbon stereocentres.

Despite a large body of literature on 1,4-conjugate additions, analogous 1,6-addition methods are underdeveloped.[4] The presence of two electrophilic sites and difficulties in controlling the regioselectivity have limited investigations on this reaction. Thus, much work on 1,6-additions has been conducted on enynones where the 1,6-acceptor carbon is sp-hybridized while the 1,4-carbon acceptor is $sp^2$-hybridized. Another approach for the control of regioselectivity is to add a bulky substituent at the 1,4-carbon acceptor to bias the system towards 1,6-addition.[5] More recently, a few reports have moved away from traditional copper catalysis to other metals for high regioselectivities. Hayashi et al. have reported the 1,6-addition of aryl boronic acids to α,β,γ,δ-unsaturated carbonyl compounds in the presence of catalytic amounts of iridium complexes.[6] The iron-catalyzed 1,6-addition of Grignard reagents to 2,4-dienoates and 2,4-dienamides has been reported by Urabe et al.[7] The reaction of aryl- and alkenylboronic acids with 2,4-dienoate esters, catalyzed by rhodium, has also been investigated.[8] There have been only two examples of asymmetric 1,6-addition reactions. Hayashi et al. have reported the Rh-catalyzed asymmetric 1,6-addition of aryltitanates to alkyne acceptors to afford chiral allenes.[9] The same group subsequently described the Rh-catalyzed asymmetric 1,6-addition of aryl zinc reagents to dienones.[10]

The addition of carbon nucleophiles in a 1,6-conjugate fashion still remains a challenging topic of great synthetic interest. Herein we report the first catalytic asymmetric 1,6-conjugate addition of dialkylzinc reagents to 5-(3-aryl-2-propenylidene) Meldrum's acid to afford tertiary and quaternary stereogenic centres.

## 2. Results and discussion

The enantioselective formation of all-carbon benzylic quaternary stereocentres via the 1,4-addition of dialkylzinc reagents to 5-(1-arylethylidene) Meldrum's acid was recently reported by our laboratory.[11] Over the course of our studies, it was observed that the increased substitution at the 2-position of the alkylidene inhibited conjugate addition. As illustrated in Scheme 1, 5-(1-phenyl-2-methylpropylidene) Meldrum's acid **1a** was inert under our optimal reaction conditions, and the starting material was quantitatively recovered. This observation indicated that the 1,4-conjugate addition pathway could be blocked effectively, and was an incentive to explore 1,6-addition to dienyl Meldrum's acids.

Next, it remained to establish that 1,6-addition would proceed on 5-(3-aryl-2-propenylidene) Meldrum's acid derivatives. Along the lines of our previous report, the formation of all-carbon benzylic quaternary stereocentres was initially

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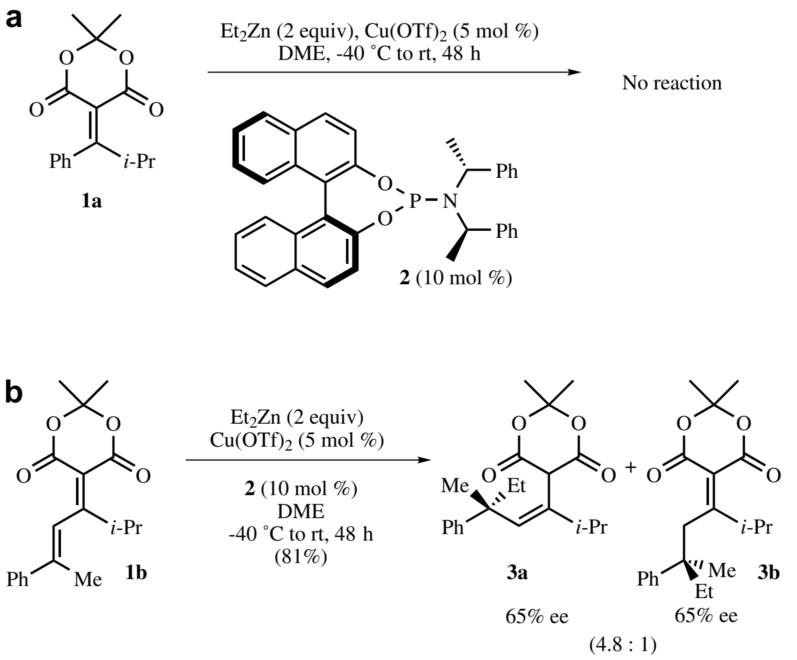
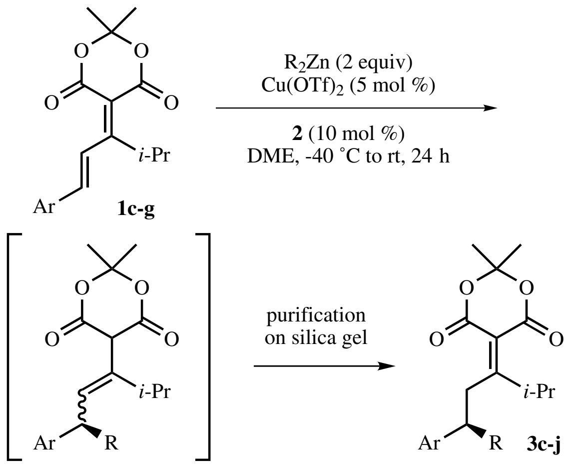
doi:10.1016/j.tetasy.2006.11.009



**Scheme 1.** Initial results.

attempted. Meldrum's acid **1b** was reacted with $Et_2Zn$ in the presence of $Cu(OTf)_2$ (5 mol %), and phosphoramidite ligand **2** (10 mol %)[12] to afford exclusively 1,6-adducts **3a** and **3b** in a 4.8:1 ratio and an 81% combined isolated yield, and in 65% enantiomeric excess (Scheme 2). The β,γ-unsaturated compound **3a** was the major component of the mixture, and alkylidene Meldrum's acid **3b** the minor. It is noteworthy that *Z*-olefin **3a** was obtained as a single isomer and the stereochemistry of the trisubstituted alkene was determined by NOE experiments.



**Scheme 2.** 1,6-Conjugate addition of dialkylzinc reagents to 5-(3-aryl-2-propenylidene) Meldrum's acids.

Our attention then turned to the formation of tertiary stereocentres.[13] When Meldrum's acid **1c** was reacted with $Et_2Zn$, **3c** was isolated in a 70% ee and a 65% yield after 24 h (Table 1, entry 1).[14] The β,γ-unsaturated product was formed initially as determined by the analysis of the $^1H$ NMR of the crude product, but readily isomerized to the corresponding alkylidene Meldrum's acid upon purification on silica gel. The alkene isomerization limited the yield in some cases as the alkylidenes decomposed during flash chromatography and upon standing. The effect of substituting the aromatic moiety on the enantioselectivity of the conjugate process was then investigated. The introduction of an electron-donating group at the 4-position furnished Meldrum's acid **3d** in a 74% ee, while electron withdrawing group at the same position gave an 84% ee (Table 1, entries 2 and 3). Furthermore, changing the ring substitution showed that meta substitution decreased ee, while there was no change between the *ortho*- and *para*-positions (Table 1, entries 3–5).

Additionally, various dialkylzinc reagents reacted with **1c** resulting in good enantioselectivities (Table 1). Dibutylzinc afforded the 1,6-adduct in an 82% ee, while sterically demanding diisopropylzinc afforded the product in a 75% ee. Dimethylzinc reagent also added smoothly to give the 1,6-product in a 83% ee.

**Table 1.**

| Entry | Ar | R | ee (%) | Yield (%) |
|---|---|---|---|---|
| 1 | Ph **1c** | Et | 70 | 65 **3c** |
| 2 | 4-MeOPh **1d** | Et | 74 | 19 **3d** |
| 3 | 4-ClPh **1e** | Et | 84 | 26 **3e** |
| 4 | 3-ClPh **1f** | Et | 60 | 50 **3f** |
| 5 | 2-ClPh **1g** | Et | 84 | 29 **3g** |
| 6 | Ph **1c** | *n*-Bu | 82 | 44 **3h** |
| 7 | Ph **1c** | *i*-Pr | 75 | 56 **3i** |
| 8 | Ph **1c** | Me | 83 | 19 **3j** |

## 3. Conclusions

In conclusion, we have reported the first asymmetric synthesis of benzylic tertiary and quaternary stereogenic centres via 1,6-conjugate addition of dialkylzinc reagents to Meldrum's acid acceptors in good yields and selectivities.

## Acknowledgments

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canadian Foundation for Innovation, the Ontario Innovation Trust, and the University of Waterloo. We gratefully acknowledge the Merck Frosst Centre for Therapeutic Research, Boehringer Ingelheim (Canada) Ltd. (Young Investigator Award to E.F.), AstraZeneca Canada Inc. (AstraZeneca Award to E.F.) for unrestricted support of this research. A.W. is indebted to NSERC for a CGS-D scholarship. E.-T.L. is grateful for NSERC URSA.

## References

1. Asymmetric 1,4-conjugate addition reviews: (a) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 224–258; (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, *67*, 3221–3236; (c) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196; (d) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061.
2. For reviews on catalytic asymmetric synthesis of all-carbon quaternary carbon centers: (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396; (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363–5367.
3. Asymmetric 1,4-conjugate addition forming all-carbon quaternary centres: (a) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417; (b) Lee, K.; Brown, K. M.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184; (c) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376–1378; (d) Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988–14989; (e) Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584–4585; (f) Mauleón, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961–4963; (g) Fuchs, N.; d'Augustin, M.; Humam, M.; Alexakis, A.; Taras, R.; Gladiali, S. *Tetrahedron: Asymmetry* **2005**, *16*, 3143–3146.
4. For reviews on 1,6-conjugate addition: (a) Krause, N.; Thorand, S. *Inorg. Chim. Acta* **1999**, *296*, 1–11; (b) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 186–204; (c) Fredrick, M. A.; Hulce, M. *Tetrahedron* **1997**, *53*, 10197–10227.
5. Marshall, J. A.; Ruden, R. A.; Hirsch, L. K.; Phillippe, M. *Tetrahedron Lett.* **1971**, *41*, 3795–3998.
6. Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1–4.
7. Fukuhara, K.; Urabe, H. *Tetrahedron Lett.* **2005**, *46*, 603–606.
8. de la Herrán, G.; Murcia, C.; Csákÿ, A. G. *Org. Lett.* **2005**, *7*, 5629–5632.
9. Hayashi, T.; Tokunaga, N.; Inoue, K. *Org. Lett.* **2004**, *6*, 305–307.
10. Hayashi, T.; Yamamoto, S.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 4224–4227.
11. Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775.
12. (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.* **1997**, *36*, 2620–2623.
13. 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.
14. Typical procedure: Conjugate 1,6-additions were carried out using 0.12 mmol of substrate. In a glove box, a flame-dried resealable Schlenk tube was charged with $Cu(OTf)_2$ (5 mol %) and ligand **2** (10 mol %). Dry DME (0.5 mL) was then added to the Schlenk tube to wash down any residual solids to the bottom. The resulting solution was allowed to stir at rt for 15 min, outside the glove box, and then cooled to −40 °C using an acetone/dry-ice bath. In a dry box, the commercially available solution of $R_2Zn$ (2.0 equiv) was transferred to a capped round-bottom flask. This solution was added to the Schlenk tube dropwise via a syringe and the resulting reaction mixture stirred for 5 min at −40 °C. A solution of freshly purified 5-(3-aryl-2-propenylidene) Meldrum's acid (1.0 equiv) in DME (0.5 mL) was then added dropwise using a syringe, and additional DME (0.2 mL) was added to rinse the sides of the Schlenk tube. This mixture was allowed to warm up slowly to ambient temperature, and stirred for 24–48 h. The reaction was quenched by the addition of a 5% HCl solution and diluted with $Et_2O$. The layers were partitioned and the aqueous layer extracted with $Et_2O$ (3×). The combined organic layers were washed with water (1×), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using a combination of EtOAc and hexanes or petroleum ether (35–60 °C) as eluent to yield the desired product. HPLC equipped with a chiral column (OD–H or AD–H) was used to measure the enantiomeric excess of the products. The racemates were prepared using the corresponding Grignard reagent (2.5 equiv) in THF at −40 °C.