Tetrahedron Letters 54 (2013) 932–935

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Diastereoselective formation of β-hydroxyketones by the reduction of Ketene dimers

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ARTICLE INFO

Article history:
Received 31 October 2012
Revised 2 December 2012
Accepted 5 December 2012
Available online 20 December 2012

Keywords:
Disubstituted ketenes
Ketoketenes
Ketene dimer
Ketene heterodimer
β-Lactones
Diastereoselective
Reduction
β-Hydroxyketones
Enolates
Chiral
Enantioenriched

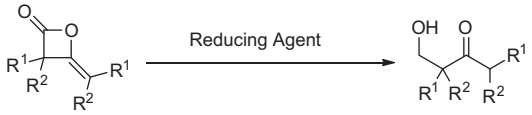
ABSTRACT

A general method for the diastereoselective formation of β-hydroxyketones by the reduction of ketene dimers was developed. The reduction of ketene homodimers, derived from alkylarylketenes and dimethylketene, and ketene heterodimers, derived from methylketene and ethylphenylketene or diphenylketene, was investigated. Methylphenylketene dimer was reduced with optimal diastereoselectivity (dr = 6:1) using $LiBH_4$. However, more generally, $LiAlH_4$ was found to be the most effective reducing system with respect to diastereoselectivity (dr up to >99:1) and yield (62–>99% for 10 examples).

Aldol reactions and their products are widely used in the synthesis of complex molecules.[1] While efficient routes exist for most classes of aldol products, successful aldol reactions involving formaldehyde are rare.[2] This is due to formaldehyde's common availability as an aqueous solution which generally precludes the use of moisture-sensitive metallating agents (e.g., $TiCl_4$). We considered that the use of a conceptually different route that involved sequential ketene dimerization-reduction would obviate the need for formaldehyde itself and open the way to a general method for the preparation of *β*-unsubstituted aldol products (Scheme 1).

A few years ago, both our group and Ye's group reported systems for the dimerization of ketoketenes (disubstituted ketenes).[3,4] In 2010, our group reported a versatile chiral phosphine catalytic system (Josiphos) which provided a general method for the asymmetric homodimerization of ketoketenes (Scheme 2).[5]

In addition, we recently described an alkaloid-catalyzed asymmetric heterodimerization of ketenes that provided access to ketene heterodimer *β*-lactone products in excellent enantiomeric excess (Scheme 3).[6] We believed that a ketene dimerization reaction, followed by a stereoselective ketene dimer reduction, would provide an efficient and diastereoselective route to aldol products derived from formaldehyde.



Scheme 1. Reduction of ketene dimers to give β-hydroxyketones.

In 1996 Calter showed that a nucleophilic catalyst system (TMS-quinine or TMS-quinidine) could catalyze the homodimerization of aldoketenes with high enantio-selectivity.[7] While reduction of aldoketene dimer β-lactones provides access to aldol products possessing one chiral center in modest yield, both our group and Ye's group noted in preliminary communications that reduction of ethylphenylketene dimer provides efficient access to an aldol product possessing two chiral centers with high diastereoselectivity (dr >99:1).[3–5] However, the scope of the reduction process had been by no means established.[3–5] In this Letter we describe our studies on the development of a diastereoselective reduction of methylphenylketene dimer, as well as a broader examination of

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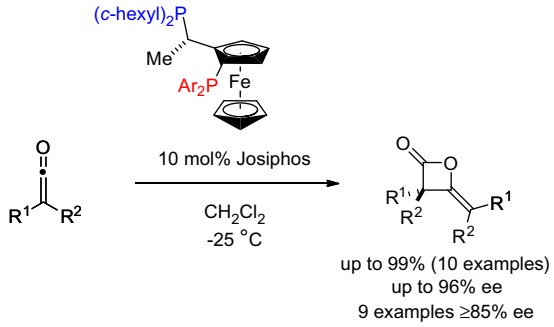
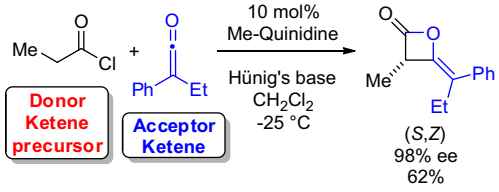
http://dx.doi.org/10.1016/j.tetlet.2012.12.011



Scheme 2. Phosphine-catalyzed asymmetric homodimerization of ketenes.

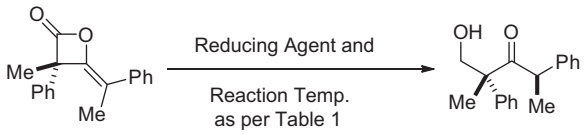


Scheme 3. Catalytic asymmetric heterodimerization of ketenes.

the substrate scope and diastereoselectivity of the reduction method.

We began our investigations with a focus on the reduction of methylphenylketene dimer, as we felt that the resulting aldol product, bearing an α-quaternary stereogenic center with a methyl substituent, would prove useful in synthetic activities (Table 1).[8] Our initially favored reducing agent, $LiAlH_4$, facilitated access to the desired product in satisfactory yield (70%) but with moderate diastereoselectivity (dr = 3:1).[9] We then proceeded to evaluate a range of common reducing agents ($NaBH_4$, DIBAL, $Zn(BH_4)_2$, $Li(t\text{-}BuO)_2AlH_2$, and $LiBH_4$). A 2.0 M solution of $LiBH_4$ in THF proved to be the most effective reducing agent in terms of both diastereoselectivity (dr 6:1) and conversion (69%). Optimal reaction conditions involved the use of 1 equiv of the $LiBH_4$ reagent solution, with the ketene dimer at a concentration of 0.25 M in THF, and with reaction quenching performed at 0 °C using aqueous saturated ammonium chloride (Table 1, entry 6).

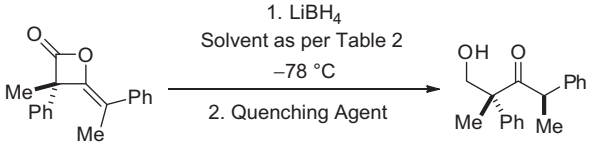
Table 1
Optimization of reduction of methylphenylketene dimer **1a** to form β-hydroxyketone **2a**[a]



Entry	Reducing agent	Yield[b] (Conv)[c]	Solvent	Temp.(°C)	dr[d]
1	$LiAlH_4$	70	THF	−78	3:1
2	$NaBH_4$	0	EtOH/H_2O	r.t.	—
3	$Li(t\text{-}BuO)_2AlH_2$	0	THF	−78	—
4	DIBAL	(67)	CH_2Cl_2	−78	5:1
5[e]	$Zn(BH_4)_2$	(40)	THF	−78	4:1
6	$LiBH_4$	(69)	THF	−78	6:1

[a] Aqueous saturated ammonium chloride added as quenching agent in most cases at 0 °C.
[b] Yields are isolated yields.
[c] Conversion (Conv) determined by GC–MS analysis of crudes.
[d] Diastereomeric ratio (dr) was determined by ^1H NMR analysis of crudes.
[e] Quenched with HCl (1 M) solution.

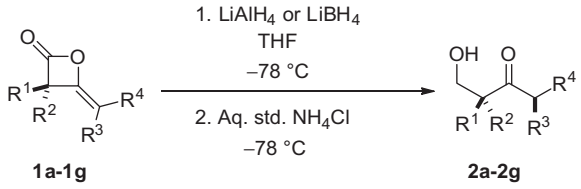
Table 2
Further optimization of reduction of methylphenylketene dimer **1a** to form **2a**[a]



Entry	Solvent	Quench temp.	Quenching Agent	Conv	dr
1	THF	0 °C	Aq std. NH_4Cl	69	6:1
2	THF	−78 °C	Aq std. NH_4Cl	76	5:1
3	THF	−78 °C	H_2O	64	2:1
4	THF/Et_2O[b]	−78 °C	Aq std. NH_4Cl	16	nd

[a] All reactions were conducted at 0.25 M concentration of dimer in solvent.
[b] Et_2O from ethereal solution of $LiBH_4$ (1.0 M in Et_2O).

Table 3
Substrate scope of the reduction of ketene dimers



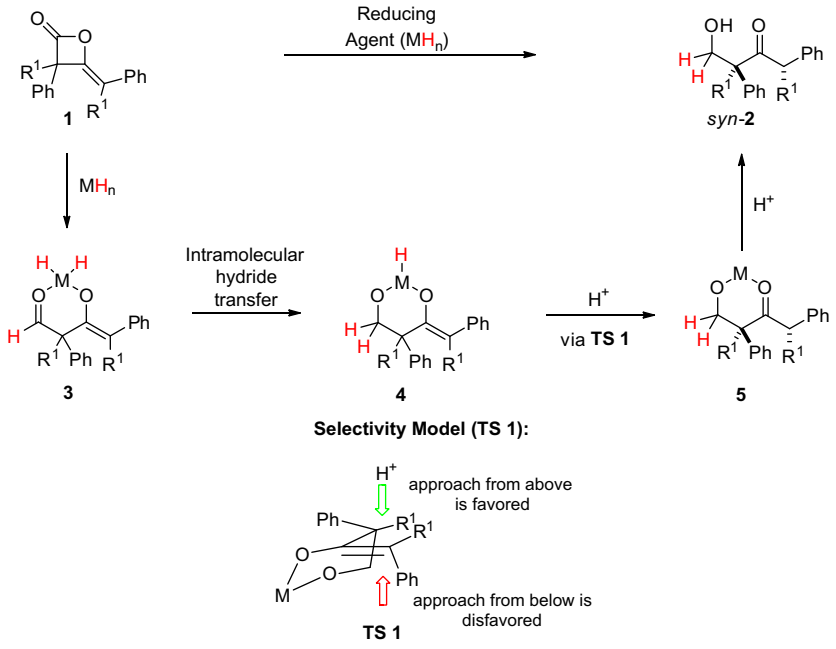
Entry	R_1	R_2	R_3	R_4	Yield[a] (conv)	dr	Product
1[b]	Me	Ph	Me	Ph	62 (76)	5:1	**2a**
2[b]	Et	Ph	Et	Ph	0	—	—
3	Et	Ph	Et	Ph	>99	>99:1	**2b**
4	Et	4-ClPh	Et	4-ClPh	(93)	7:1	**2c**
5	*n*-Bu	Ph	*n*-Bu	Ph	75	7:1	**2d**
6	Me	Me	Me	Me	94	—	**2e**
7[c]	H	Me	Ph	Ph	92	—	(−)-**2f**
8[d]	Me	H	Ph	Ph	90	—	(+)-**2f**
9	Me	H	Et	Ph	35 (69)	2:1	**2g**

[a] Yields are isolated yields.
[b] $LiBH_4$ was used.
[c] For the (−)-enantiomer.
[d] For the (+)-enantiomer.

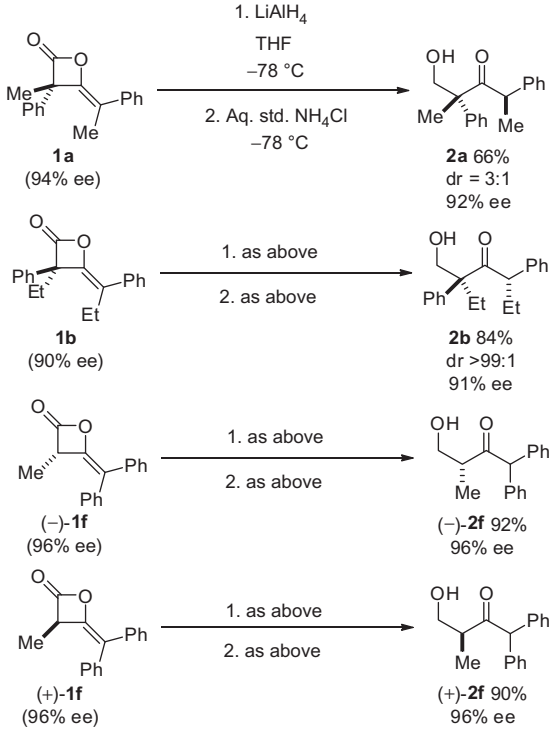
Quenching the reaction at −78 °C (Table 2) led to no improvement in dr with only a slight improvement in conversion observed (76%). The selection of saturated aqueous ammonium chloride as quenching agent, rather than water, was found to provide optimal results in terms of both diastereoselectivity and yield (Table 2 entry 2 vs entry 3). The use of diethyl ether as co-solvent (when a 1.0 M ethereal solution of $LiBH_4$ was used as reagent) had a dramatic deleterious effect on the reaction (entry 4). The use of less than 1 equiv of $LiBH_4$ (e.g., 0.5 equiv, 14% conv) or more dilute reaction conditions (e.g., 0.15 M ketene dimer in THF, 60% conv) led to lower conversions.

We then investigated the $LiBH_4$ reducing system with ethylphenylketene dimer. However, unfortunately it gave poor results (Table 3, entry 2) and so we revisited $LiAlH_4$ as a reducing agent for all other substrates (Table 3, entries 3–9).[10,11]

Using the $LiAlH_4$ reducing system, good yields and diastereoselectivities were obtained in the reduction of ketene homodimers (entries 3–6) and also ketene heterodimers (entries 7–9). The major diastereomer in each case was assigned to be the *syn*-diastereomer by analogy with Ye's work.[4] Intermolecular proton quenching (by added aqueous NH_4Cl solution) of enolate **4**, explains the observed sense of diastereoselectivity (*syn*). A chelate of both oxygens to aluminum or boron (M = Al or B) would hinder approach of the proton source to the lower face of the enolate **4** in TS 1



Scheme 4. Possible mechanism for the formation of **2** as the *syn*-diastereomer (ligands on M in **5** and TS 1 omitted for clarity).



Scheme 5. Reduction of enantioenriched ketene dimers to give enantioenriched β-hydroxyketones.

(Scheme 4). Therefore protonation of the upper face of the enolate **4** is favored. Lower diastereoselectivity obtained in entry 1, Table 1 and entry 9, Table 3 might be explained by non-selective protonation of enolate **4** through competing transition states, in those cases where a more reactive, less sterically hindered enolate (e.g., R^1 = Me) presents itself.

Retention of chirality during $LiAlH_4$-reduction of our enantioenriched ketene dimers was also investigated (Scheme 5).[5,6] Enantioenriched **1a** (94% ee), **1b** (90% ee), (+)-**1f,** and (−)-**1f** were all reduced effectively and without significant loss of enantiomeric integrity to give enantioenriched **2a** (92% ee), **2b** (91% ee), (+)-**2f** (96% ee), and (−)-**2f** (96% ee), respectively (Scheme 5). Therefore the present method provides a valuable route to enantioenriched β-hydroxyketones from readily available ketene dimers.[3–6]

In summary, we have evaluated reduction of ketene dimers as a route to β-hydroxyketones and determined that lithium aluminum hydride is the most general reducing agent with respect to substrate scope and diastereoselectivity, although lithium borohydride works best for the reduction of methylphenylketene dimer.

Acknowledgments

We thank the National Science Foundation (Grant Nos. CHE-0911483 and CHE-1213638 to N.J.K., CHE-0821487 for NMR facilities at Oakland University, and CHE-1048719 for LC-MS facilities at Oakland University).

Supplementary data

Supplementary data (characterization data and procedures for the preparation of β-hydroxyketones **2a**–**2g**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.011.

References and notes

1. (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 111; (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1–115; (c) Mukaiyama, T. *Org. React.* **1982**, *28*, 203–331; (d) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489–503; (e) Calter, M. A.; Liao, W.; Struss, J. A. *J. Org. Chem.* **2001**, *66*, 7500–7504; (f) Calter, M. A.; Liao, W. *J. Am. Chem. Soc.* **2002**, *124*, 13127–13129.
2. Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590–3596. and references cited therein.
3. (a) Ibrahim, A. A.; Harzmann, G. D.; Kerrigan, N. J. *J. Org. Chem.* **2009**, *74*, 1777–1780; (b) Ibrahim, A. A.; Smith, S. M.; Henson, S.; Kerrigan, N. J. *Tetrahedron Lett.* **2009**, *50*, 6919–6922; (c) Wei, P.-H.; Ibrahim, A. A.; Mondal, M.; Nalla, D.; Harzmann, G. D.; Tedeschi, F. A.; Wheeler, K. A.; Kerrigan, N. J. *Tetrahedron Lett.* **2010**, *51*, 6690–6694.
4. Lv, H.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Adv. Synth. Catal.* **2008**, *350*, 2715–2718.

5. Ibrahim, A. A.; Wei, P.-H.; Harzmann, G. D.; Kerrigan, N. J. *J. Org. Chem.* **2010**, *75*, 7901–7904.
6. Ibrahim, A. A.; Nalla, D.; Van Raaphorst, M.; Kerrigan, N. J. *J. Am. Chem. Soc.* **2012**, *134*, 2942–2945.
7. (a) Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006–8007; (b) Calter, M. A.; Orr, R. K. *Org. Lett.* **2003**, *5*, 4745–4748.
8. (a) Rasmussen, K.; Calligaro, D. O.; Czachura, J. F.; Dreshfield-Ahmad, L. J.; Evans, D. C.; Hemrick-Luecke, S. K.; Kallman, M. J.; Kendrick, W. T.; Leander, J. D.; Nelson, D. L.; Overshiner, C. D.; Wainscott, D. B.; Wolff, M. C.; Wong, D. T.; Branchek, T. A.; Zgombick, J. M.; Xu, Y.-C. *J. Pharmacol. Exp. Ther.* **2000**, *294*, 688–700; (b) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043–14053.
9. *Experimental procedure using $LiAlH_4$ for preparation of* ***2a***: To methylphenylketene dimer **1a** (57 mg, 0.21 mmol) was added $LiAlH_4$ (1 M in Et_2O, 0.21 mL, 0.21 mmol) at −78 °C. The reaction was quenched with aqueous saturated NH_4Cl solution (5 mL) at −78 °C. The resulting crude product **2a** had a dr = 3:1 as determined by ^1H NMR analysis. Crude **2a** was purified by a flash column chromatography over neutral silica (iatrobeads), eluting with a gradient solvent system (from hexane to 5% EtOAc/hexane) of neutral silica (iatrobeads). The solvent was removed under reduced pressure to afford (±)-**2a** as a white solid (40 mg, 70%) and as a single diastereomer.
10. *Selected characterization data for* ***2a***: IR (thin film): 3428, 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, TMS): δ 7.40–7.11 (m, 10H), 4.02 (d, J = 11.6 Hz, 1H), 3.65 (q, J = 10.3 Hz, 1H), 3.35 (d, J = 11.6 Hz, 1H), 2.35 (s, 1H), 1.35 (s, 3H), 1.16 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 215.3, 141.4, 139.2, 129.2, 128.9, 128.0, 127.8, 127.1, 127.1, 70.1, 59.1, 48.8, 22.1, 18.3; (M^++Na)HRMS m/z Calcd for $C_{18}H_{20}O_2Na$: 291.1356; found: 291.1349.
11. *Experimental procedure using $LiBH_4$ for preparation of* ***2a***: Methylphenylketene dimer **1a** (0.44 mmol) was dissolved in THF (1.8 mL) and the solution was cooled to −78 °C. $LiBH_4$ (2.0 M in THF, 0.22 mL, 0.44 mmol) was added to the cooled solution at −78 °C. The reaction was allowed to warm to room temperature and stirred until TLC showed complete consumption of starting material (ca. 80 min). The reaction was then cooled to −78 °C and was quenched with aqueous saturated NH_4Cl solution (10 mL) at −78 °C. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford β-hydroxyketone **2a** as a white solid (73 mg, 62%) with ⩾94% purity and dr = 5:1 as determined by ^1H NMR and GC–MS analysis.