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Direct Asymmetric Allylic Alkylation of Butenolides with Morita−Baylis−Hillman Carbonates

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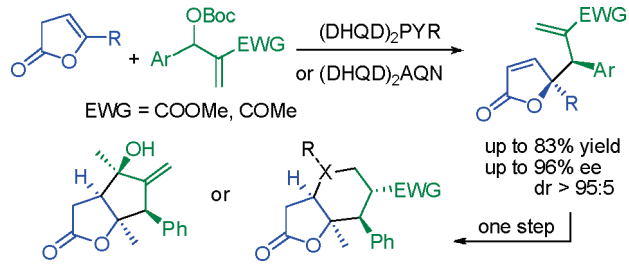
ABSTRACT



The direct asymmetric allylic alkylation of β,γ-butenolides with MBH carbonates to access γ,γ-disubstituted butenolides containing adjacent quaternary and tertiary chiral centers has been presented in excellent stereoselectivities (86−96% ee, dr >95:5) and moderate to good yield (50−83%). Their synthetic utility has been well demonstrated by the facile construction of bicyclic lactones bearing 4−5 stereogenic centers.

The widespread occurrence of the butenolide unit in natural products and pharmaceutically useful molecules has long stimulated efforts on its synthesis and transformations.[1] Thus, the development of enantioselective protocols to access functionalized butenolides has triggered increasing interest in this regard.[2] Most literature procedures have been focused on the Mukaiyama-type additions that were limited to the applications of preformed silyloxyfurans.[3] However, in view of atom economy, the direct modification of butenolides represents a more attractive approach, which enables synthetic convenience and efficiency. Shibasaki[4a] and Trost[4b] reported their pioneering work in the field of direct enantioselective functionalization of butenolides, although only simple butenolides have been tested. Recently Buchwald and co-workers presented the synthesis of γ,γ-disubstituted butenolides involving the construction of a quaternary carbon center via direct γ-arylation of γ-substituted butenolides.[5] Nevertheless, to the best of our knowledge, no

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(1) For a review on natural products containing the butenolide unit, see: (a) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504. For reviews on the synthesis of butenolides, see: (b) Rao, Y. S. *Chem. Rev.* **1964**, *64*, 353. (c) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707. (d) Montagnon, T.; Tofi, M.; Vassilikogiannakis, G. *Acc. Chem. Res.* **2008**, *41*, 1001.

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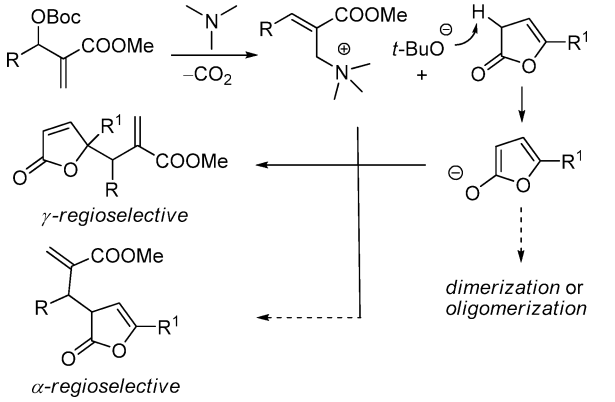
report has yet been published on the direct asymmetric variant of these easily prepared but useful γ-substituted butenolides.[6]

Recently, the allylic alkylation with Morita−Baylis−Hillman (MBH) adducts by the catalysis of metal-free Lewis basic tertiary amines or phosphines has emerged as a powerful strategy to deliver multifunctional compounds.[7,8] Krische[9a] reported the first phosphine-catalyzed allylic alkylation of 2-silyloxyfuran with MBH acetates in excellent regio- and diastereoselectivities. Later Shi[9b] developed the first asymmetric variant to afford γ-substituted butenolides by employing newly designed chiral bifunctional phosphine catalysts. However, limitation of substrate to preformed 2-silyloxyfuran without any substitution incapacitated access to enantioenriched γ,γ-disubstituted butenolides. We envisioned that, as outlined in Scheme 1, the direct tertiary amine-catalyzed

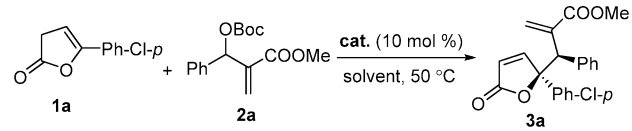
Scheme 1. Proposed Direct Allylic Alkylation of γ-Substituted Butenolides with MBH Carbonates



asymmetric γ-allylic alkylation of γ-substituted butenolides would be realized via deprotonation by an *in situ* generated *tert*-butoxy anion and subsequent vinylogous addition reaction. We wondered whether the chemo-, regio-, and stereoselectivities could be well accomplished simultaneously, although the rather challenging construction of adjacent quaternary and tertiary chiral centers must be fulfilled.[10,11]

We began our investigation with the reaction of β,γ-butenolide **1a** bearing a γ-aryl substitution with MBH carbonate **2a** in the presence of DABCO (20 mol %) in DCE at ambient temperature. To our delight, the reaction proceeded very smoothly, and the regioselective γ,γ-disubstituted butenolide **3a** was obtained with excellent diastereoselectivity (>95:5)[12] in 88% yield after 1 h, although some unidentified byproduct was also observed (Table 1, entry 1). We then examined the asymmetric catalytic ability of some modified cinchona alkaloids at higher temperature (entries 2−6).[13] The screening studies revealed that $(DHQD)_2PYR$ was the best choice in terms

Table 1. Screening Studies of Direct Asymmetric Allylic Alkylation of β,γ-Butenolides **1a** with MBH Carbonate **2a**[a]



entry	catalyst[b]	solvent	t (h)	yield[c] (%)	ee[d] (%)
1[e]	DABCO	DCE	1	88	
2	$(DHQD)_2AQN$	DCE	19	61	83
3	$(DHQD)_2PHAL$	DCE	24	66	81
4	$(DHQD)_2PYR$	DCE	18	90	85
5	$(DHQ)_2AQN$	DCE	24	35	−10
6	$(DHQ)_2PYR$	DCE	25	65	−35
7	$(DHQD)_2PYR$	toluene	32	60	91
8	$(DHQD)_2PYR$	$PhCF_3$	22	78	92
9[f]	$(DHQD)_2PYR$	$PhCF_3$	47	62	93
10[g]	$(DHQD)_2PYR$	$PhCF_3$	54	54	92
11[h]	$(DHQD)_2PYR$	$PhCF_3$	10	82	92
12[h]	$(DHQ)_2PYR$	$PhCF_3$	19	45	−46

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **1a**, 0.2 mmol of **2a**, and 10 mol % of catalyst in 1.0 mL of solvent at 50 °C. [b] DABCO: 1,4-diazabicyclo[2.2.2]octane. $(DHQD)_2AQN$: hydroquinidine (anthraxquinone-1,4-diyl) diether. $(DHQD)_2PHAL$: hydroquinidine 1,4-phthalazinediyl diether. $(DHQD)_2PYR$: hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether. $(DHQ)_2AQN$: hydroquinineanthraxquinone-1,4-diyl diether. $(DHQ)_2PYR$: hydroquinine-2,5-diphenyl-4,6-pyrimidinediyl diether. [c] Isolated yield of pure **3a** (dr >95:5).[12] [d] Determined by chiral HPLC analysis. [e] At rt, with 20 mol % of catalyst. [f] At 35 °C. [g] 10 mol % of *S*-BINOL was added. [h] In 0.5 mL of solvent.

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(10) For reviews on the construction of a quaternary carbon center, see: (a) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (b) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (c) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583.

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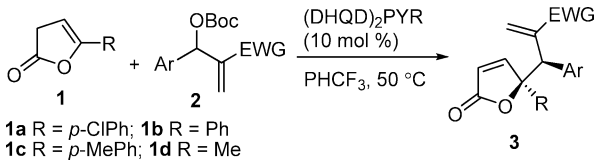
(12) The diastereomeric ratio of >95:5 indicates that the minor isomer could not be detected by ^1H NMR analysis. Excellent diastereoselectivities (generally >95:5) were reported in the similar reaction of 2-silyloxyfuran by Krische and Shi; see ref 9.

(13) For reviews, see: (a) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (b) Gaunt, M. J.; Johansson, C. C. C. *Chem. Rev.* **2007**, *107*, 5596.

of enantioselectivity and yield (entry 4). However, much inferior stereocontrol was attained in the presence of tertiary amines derived from DHQ, and the products possessed the opposite configuration (entries 5 and 6). Subsequently, the optimization of other reaction parameters (solvent, temperature, additive, concentration, etc.) was continued with $(DHQD)_2PYR$ (entries 7−11). It was found that better results were gained when $PhCF_3$ was applied as the solvent (entry 8), but neither lowering the temperature nor adding 10 mol % of *S*-BINOL could improve the data (entries 9 and 10). Finally, the best results with respect to reaction efficacy, yield, and enantioselectivity were achieved by performing the reaction in a higher concentration, affording **3a** in 82% yield and 92% ee in 10 h (entry 11). Nevertheless, the enantioselectivity was still not satisfying when $(DHQ)_2PYR$ was applied (entry 12).

Consequently, more experiments to examine substrate scope and limitations under the optimized conditions were conducted. The allylic alkylation products were generally isolated as a single diastereomer. As summarized in Table 2, excellent

Table 2. Direct Asymmetric Allylic Alkylation of β,γ-Butenolides **1** with MBH Carbonates **2**[a]



1a R = *p*-ClPh; **1b** R = Ph
1c R = *p*-MePh; **1d** R = Me

entry	1	Ar	EWG	*t* (h)	yield[b] (%)	ee[c] (%)
1	**1a**	Ph	CO_2Me	10	**3a**, 82	92
2	**1b**	Ph	CO_2Me	24	**3b**, 60	91
3	**1c**	Ph	CO_2Me	14	**3c**, 76	92
4	**1d**	Ph	CO_2Me	18	**3d**, 67	80
5[d]	**1d**	Ph	CO_2Me	18	**3d**, 83	88
6[d,e]	**1d**	Ph	CO_2Me	68	**3d**, 70	88
7	**1a**	*p*-ClC_6H_4	CO_2Me	19	**3e**, 66	92
8	**1b**	*m*-ClC_6H_4	CO_2Me	12	**3f**, 68	90
9	**1a**	*o*-BrC_6H_4	CO_2Me	25	**3g**, 61	94
10	**1a**	*p*-$MeOC_6H_4$	CO_2Me	35	**3h**, 50	94
11	**1a**	*m*-MeC_6H_4	CO_2Me	23	**3i**, 62	89[f]
12	**1a**	2-thienyl	CO_2Me	18	**3j**, 68	88
13[g]	**1a**	Ph	$COCH_3$	19	**3k**, 57	96
14[g]	**1a**	*p*-BrC_6H_4	$COCH_3$	26	**3l**, 67	86
15[d,g]	**1d**	Ph	$COCH_3$	18	**3m**, 68	93

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **1**, 0.2 mmol of **2**, 10 mol % of $(DHQD)_2PYR$ in 0.5 mL $PHCF_3$ at 50 °C. [b] Isolated yield of pure **3** (dr >95:5).[12] [c] Based on chiral HPLC analysis. [d] With $(DHQD)_2AQN$ in DCE. [e] At 1.0 mmol scale with 2 mol % of catalyst loading. [f] The absolute configuration of **3i** was determined by X-ray analysis (see Figure 1). The other products were assigned by analogy. [g] At 35 °C.

enantioselectivities and moderate to good yields (60−82%) were obtained for a few β,γ-butenolides **1a**−**1c** bearing different γ-aryl groups in the reaction with MBH carbonate **2a** (Table 2, entries 1−3). It was pleasing that a simple γ-methyl-substituted butenolide **1d** exhibited good reactivity (entry 4), and higher enantioselectivity and yield were obtained by the catalysis of $(DHQD)_2AQN$ in DCE (entry 5). It was noteworthy that the reaction could be conducted at lower catalyst loading (2 mol %) without affecting the high enantioselectivity (entry 6). On the other hand, excellent enantiocontrol (88−94% ee) was attained for a diversity of MBH carbonates with various electron-deficient or -rich aryl or heteroaryl groups, generally in fair to good yields (50−68%) (entries 7−12). In addition, the MBH carbonates derived from methyl vinyl ketone (MVK) also led to the corresponding γ,γ-disubstituted butenolides in high enantioselectivities (entries 13−15). Unfortunately, a messy reaction was noted for MBH carbonates with a β-alkyl substitution.

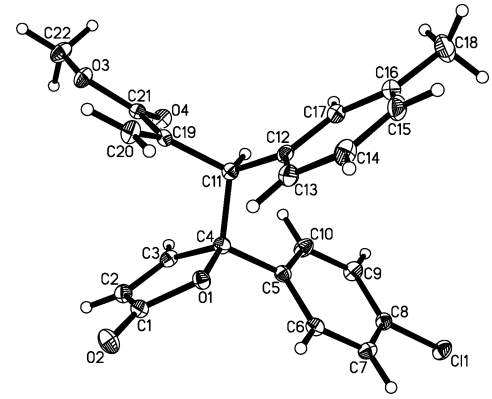
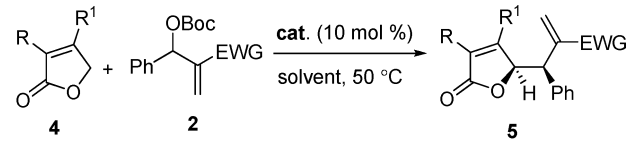


Figure 1. ORTEP representation of the X-ray structure of enantiopure **3i** (thermal ellipsoids at 30% probability).

Moreover, we intended to expand the substrate scope to α,β-butenolides. We were pleased to find DABCO still could promote the highly regio- and diastereoselective allylic alkylation of α,β-butenolide **4a** and MBH carbonate **2a** to provide γ-substituted butenolide **5a** in 49% yield at 50 °C, although more side reactions were observed (Table 3, entry 1). Subse-

Table 3. Direct Asymmetric Allylic Alkylation of α,β-Butenolides **4** with MBH Carbonates **2**[a]



4a R = Ph, R^1 = Me **4c** R = H, R^1 = Et
4b R = H, R^1 = *i*-Pr **4d** R = H, R^1 = H

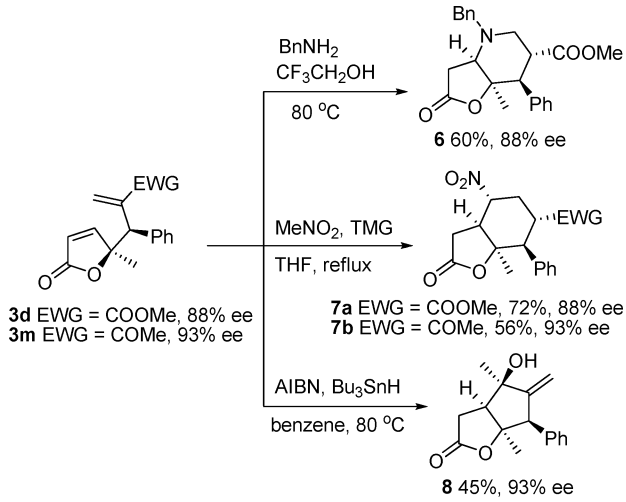
entry	catalyst	4	solvent	*t* (h)	yield[b] (%)	ee[c] (%)
1	DABCO	**4a**	DCE	24	**5a**, 49	
2	$(DHQD)_2PYR$	**4a**	$PhCF_3$	94	**5a**, 44	67
3	$(DHQD)_2PYR$	**4a**	toluene	43	**5a**, 18	68
4	$(DHQD)_2PYR$	**4a**	DCE	43	**5a**, 45	83
5	$(DHQD)_2PHAL$	**4a**	DCE	43	**5a**, 33	88
6	$(DHQD)_2AQN$	**4a**	DCE	43	**5a**, 57	90
7	$(DHQD)_2AQN$	**4b**	DCE	67	**5b**, 39	89
8	$(DHQD)_2AQN$	**4c**	DCE	40	**5c**, 38	90
9[d]	$(DHQD)_2AQN$	**4d**	DCE	24	**5d**, 24	95

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **4**, 0.2 mmol of **2a**, and 10 mol % of catalyst in 0.5 mL solvent. Entries 1−8: EWG = CO_2Me; entry 9: EWG = COMe [b] Isolated yield of pure **5** (dr >95:5).[12] [c] Determined by chiral HPLC analysis. [d] With 0.3 mmol of **4d**, 0.1 mmol of **2a**.

quently, the asymmetric screening experiments were performed (entries 2−6), and high enantioselectivity could be obtained with catalysis by $(DHQD)_2AQN$ in DCE (entry 6). Under the optimized conditions, β-substituted butenolides **4b** and **4c** afforded the allylic products with high ee values in fair yields (entries 7 and 8). The simple α,β-butenolide **4d** could react with MBH carbonate derived from MVK to give the adduct **5d** with an excellent ee value but in poor yield,[9,14] due to self-dimerization and other complex side reactions (entry 9).[1b]

We have further explored the transformations of the obtained butenolides with multiple functionalities in order to illustrate their synthetic versatility. As illustrated in Scheme 2, tandem double aza-Michael additions of benzylamine to **3d** were easily realized to provide bicyclic piperidine derivative **6** in excellent diastereocontrol (dr >95:5).[15] In addition, the highly diastereoselective tandem Michael additions with nitromethane were also quite successful by the catalysis of tetramethylguanidine (TMG), giving bicyclic lactones **7a** and **7b** with five contiguous chiral centers.[16] We investigated the intramolecular ketyl coupling reaction of **3m** via radical cyclization induced by tributyltin hydride.[17] An interesting reductive Michael addition was observed at the ketone carbonyl carbon, affording bicyclic alcohol **8** as a single isolable isomer with two quaternary chiral centers.[18] We expect that these multifunctional compounds might have potentials in the design and synthesis of biologically active or natural product like materials.

Scheme 2. Synthetic Transformation of Multifunctional Butenolides



In conclusion, we have developed the first direct asymmetric γ-allylic alkylation of butenolides with MBH carbonates promoted by modified cinchona alkaloids. This methodology exhibits high chemo-, regio-, and diastereoselectivities and allows access to γ,γ-disubstituted butenolides containing adjacent quaternary and tertiary stereogenic centers from β,γ-butenolides in excellent stereoselectivities (86−96% ee, dr >95:5) and moderate to good yields (50−83%). It could be extended to the direct asymmetric allylic alkylation of α,β-butenolides, affording similar adducts with high enantioselectivities, albeit in low to fair yields. The synthetic utility of this strategy has been demonstrated by the facile construction of bicyclic lactones containing 4−5 stereogenic centers. Their further application to the synthesis of biologically important molecules is underway in our laboratory.

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Supporting Information Available: Experimental procedures, structural proofs, NMR spectra and HPLC chromatograms of the products, and CIF file of enantiopure **3i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The obtained stereochemistry is consistent with that observed when catalysis by triphenylphosphine is employed; see ref 9a.

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(16) For examples with related frameworks, see: (a) Fuchs, S.; Berl, V.; Lepoittevin, J.-P. *Eur. J. Org. Chem.* **2007**, 1145. (b) Maulide, N.; Markó, I. E. *Chem. Commun.* **2006**, 1200. (c) Zhang, W.; Romo, D. *J. Org. Chem.* **2007**, *72*, 8939. (d) Huber, R. S.; Jones, G. B. *J. Org. Chem.* **1992**, *57*, 5778.

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