EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201301383

Highly Diastereoselective Esterification of Ketenes Generated In Situ from Acyl Chlorides with (*R*)-Pantolactone Derivatives

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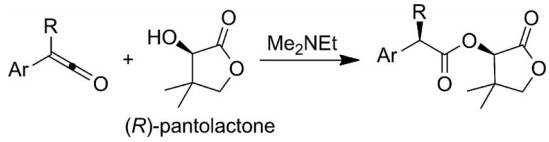
Keywords: Asymmetric synthesis / Chiral auxiliaries / Esterification / Hydrogen bonds / Ketenes

Our mechanistic investigations have revealed that Et_3N is a key requirement for the highly diastereoselective formation of esters from the corresponding acyl chlorides with (*R*)-pantolactone via ketene-derived complexes. Furthermore, we have discovered that (*R*)-*N*-benzyl-pantolactam is a more effective chiral alcohol than (*R*)-pantolactone for the esterification of in situ generated ketenes.

Introduction

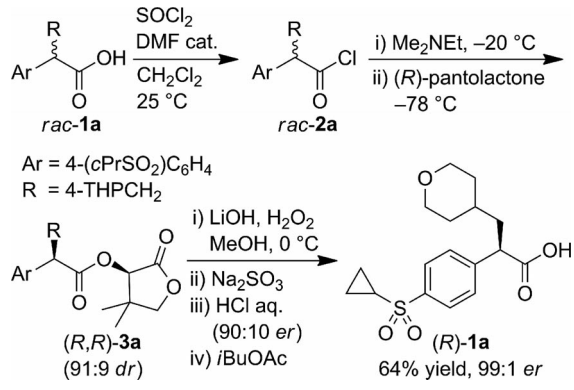
Optically active α-arylpropionic acids and their derivatives are versatile chiral building blocks in the synthesis of pharmaceuticals.[1] In 1989 Larsen et al. reported a synthesis of an α-arylpropionic acid class of nonsteroidal anti-inflammatory drugs (ibuprofen and naproxen) by asymmetric esterification of ketenes prepared in situ from the corresponding racemic carboxylic acids with (*R*)-pantolactone [Equation (1)].[2,3] Since then, various methods for ketene esterification have been reported; however, few chiral alcohols other than (*R*)-pantolactone effectively undergo asymmetric addition to ketenes.[3,4] Thus, (*R*)-pantolactone is still used as a potent auxiliary for the preparation of chiral α-arylpropionic acids by ketene esterification followed by hydrolysis, with studies revealing that the stereoselectivity of the process is strongly influenced by the ketene involved.[3,5] Although optimization by the random screening of Larsens' conditions can enhance the (*R*)-pantolactone selectivity, to date, the critical factor influencing the selectivity of the reaction is unclear. In this context, we describe mechanistic insights into the diastereoselective formation of esters derived from ketenes and (*R*)-pantolactone, highlighting the fact that Et_3N is a key to high diastereoselectivity. We also report an excellent approach to the asymmetric synthesis of α-arylpropionic acids by using (*R*)-*N*-benzyl-pantolactam.



(1)

Results and Discussion

The asymmetric synthesis of (*R*)-2-[4-(cyclopropylsulfonyl)phenyl]-3-(tetrahydropyran-4-yl)propionic acid [(*R*)-**1a**; Scheme 1] has been achieved by ketene esterification using (*R*)-pantolactone.[6,7] Our optimized conditions, in which Et_3N was used instead of Me_2NEt, gave the ester with higher diastereoselectivity (–10 °C, 91:9 *dr*; –40 °C, 94:6 *dr*; –78 °C, 97:3 *dr*); however, the selectivity was clearly lower than that obtained with nonfunctionalized compounds (up to >99:1 *dr*).[2] To elucidate the factors influencing the stereoselectivity of the synthesis of ester (*R*,*R*)-**3a**, we studied the reactions of a deuterium-labeled substrate in the presence of Et_3N (Table 1).



Scheme 1. Asymmetric synthesis of (*R*)-**1a**.

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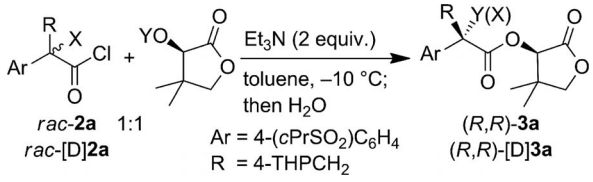
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301383.

Table 1. Deuterium-labeling experiments.[a]



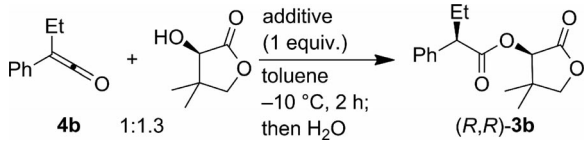
Entry	X	Y	*T* [°C]	Time [h]	*dr*[b] (Yield [%])[b] Y-(*R*,*R*)-**3a**	X-(*R*,*R*)-**3a**
1	H	D[c]	–10	2	17:1 (83)	3:1 (7)
2	H	D[c]	–80	2	>99:1[d] (78)	3:1 (7)
3[e]	H	D[c]	–10	12	6:1 (61)	2:1 (24)
4[f]	D[g]	H	–10	16	16:1 (39)	2.4:1 (16)

[a] Et_3N was added to a *rac*-**2a** solution at –10 °C. After stirring the mixture for 0.5 h, a solution of (*R*)-[D]pantolactone was added dropwise at –10 or –80 °C. [b] Determined by ^1H NMR spectroscopy. [c] 97% D. [d] (*S*,*R*)-[D]**3a** was not detected by ^1H NMR spectroscopy. [e] NaH and 15-crown-5 were added to a mixture of *rac*-**2a** and Et_3N in toluene. After stirring the mixture for 1 h, a solution of (*R*)-[D]pantolactone was added dropwise at –10 °C. [f] Et_3N was added to a solution of *rac*-[D]**2a** and (*R*)-pantolactone at –10 °C. [g] 96% D. *c*Pr = cyclopropyl, 4-THP = tetrahydro-2*H*-pyran-4-yl.

When acyl chloride *rac*-**2a** was treated with deuterium-labeled (*R*)-pantolactone (97% D) at –10 °C in toluene, deuteriated ester (*R*,*R*)-[D]**3a** with higher stereoselectivity and a small amount of protonated ester (*R*,*R*)-**3a** with lower selectivity were obtained (Entry 1).[8] Thus, the pantolactonyl ester is formed highly stereoselectively mainly because of selective proton transfer from the alcohol, but the degree of selectivity is likely limited by another proton source other than the alcohol. A lower temperature enhanced the stereoselectivity of the protonation by the alcohol proton and gave a small amount of (*S*,*R*)-[D]**3a**; however, it did not suppress protonated ester formation (Entry 2). To suppress the participation of another proton, that is, the one derived by dehydrochlorination of the acyl chloride, we treated the reaction mixture with NaH and 15-crown-5 as well as (*R*)-[D]pantolactone (Entry 3). This deprotonation led to a reduction of the ratio of the ester protonated by (*R*)-pantolactone.[9,10] However, when the acyl chloride with deuterium at the α-carbon atom (*rac*-[D]**2a**, 96% D) was treated with (*R*)-pantolactone, the ester was protonated by the alcohol with almost the same selectivity as observed for the formation of the deuteriated ester (Entry 1), although its yield was lower than that of the unlabeled *rac*-**2a** (Entry 4). These results indicate that the acidity of the α-position of *rac*-**2a** and participation of the α-proton affect the diastereoselective formation of ester (*R*,*R*)-**3a** derived from acyl chloride and (*R*)-pantolactone in the presence of Et_3N.

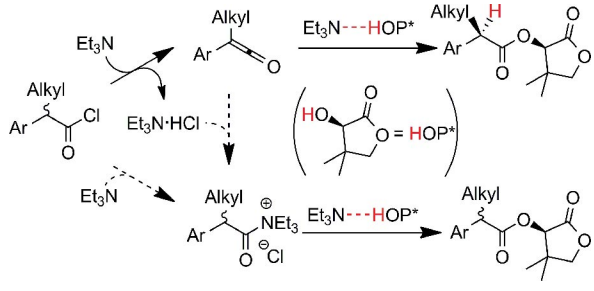
Use of an isolated ketene as a substrate instead of one generated in situ revealed the factors influencing the selectivity (Table 2). Use of nonfunctionalized ketene **4b** without an amine gave only a small amount of ester (*R*,*R*)-**3b** with low selectivity (Entry 1). Addition of tertiary trialkylamines (Et_3N or Me_2NEt) gave the ester with high diastereoselectivity (Entries 2 and 3). Even sp^2-hybridized pyridine, which showed no selectivity with *rac*-**2b**, gave the ester with significant selectivity (Entry 4). These results indicate that the highly selective formation of (*R*,*R*)-**3b** from *rac*-**2b** with Et_3N is achieved largely by the conversion of acyl chlorides into ketenes, whereas less bulky Me_2NEt and less basic, nucleophilic pyridine tend to convert the acyl chloride into an activated acylammonium salt, in whole or in part. Thus, the selectivity for (*R*,*R*)-**3b** from *rac*-**2b** by using Me_2NEt or pyridine was lower than that achieved with isolated ketene **4b** (Scheme 2). Unfortunately, the use of Et_3N·HCl led to a decrease in yield and selectivity, which explains that Et_3N·HCl has little effect on the reaction progress (Entry 5).[11,12] The formation of small amounts of ester would have indicated that a portion of Et_3N·HCl dissociates to release the free amine, which would function as a catalyst to promote the reaction. In contrast, treatment of (*R*)-pantolactone with NaH and Et_3N·HCl facilitated diastereoselective esterification, although the selectivity was lower (Entry 6),[13] which indicates that the activation of (*R*)-pantolactone is essential for the reaction and demonstrates that an alkoxide path via the enolate is not very highly selective. The decrease observed in selectivity in Entries 4 and 6 is likely due to a loss of hydrogen-bonding interactions between the alcohol of (*R*)-pantolactone and Et_3N in the

Table 2. Esterification of isolated ketene with (*R*)-pantolactone.[a]



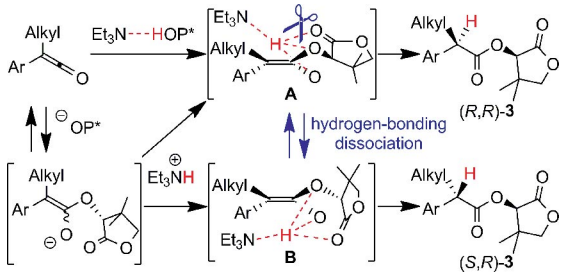
Entry	Additive	Yield [%][b]	*dr*[c]
1	none	<1[c]	1.2:1
2	Et_3N	87 (88)[d]	49:1 (24:1)[d]
3	Me_2NEt	90 (85)[d]	49:1 (1.4:1)[d]
4	pyridine	51 (83)[d]	6:1 (1:1)[d]
5	Et_3N·HCl	8	24:1
6[e]	Et_3N·HCl	64	6:1

[a] An (*R*)-pantolactone solution was added dropwise to a mixture of **4b** and additive in toluene at –10 °C. [b] Isolated yield based on **4b**. [c] Determined by ^1H NMR spectroscopy. [d] Values in parentheses are results obtained with **4b** prepared in situ from acyl chloride *rac*-**2b** with additive (2 equiv.). [e] NaH was added to an (*R*)-pantolactone solution. After stirring the mixture for 1 h, **4b** and Et_3N·HCl were added stepwise at –10 °C.



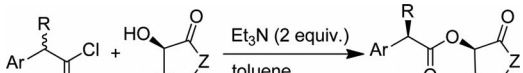
Scheme 2. Proposed mechanism for diastereoselective esterification via activated species derived from acyl chloride.

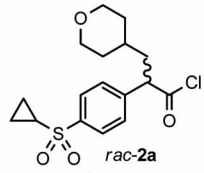
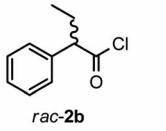
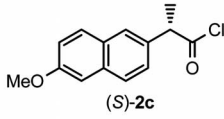
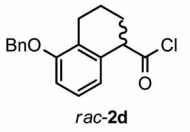
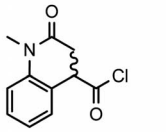
transition state.[14] Cannizzaro and Houk used a computational approach to predict that highly stereoselective tautomerization to an ester can be achieved through a high rotational barrier for the conformational equilibrium between ketene acetals **A** and **B** derived from a ketene and an (*R*)-pantolactone–amine complex



Scheme 3. Proposed mechanism for stereoselective formation of ketene acetals through hydrogen bonding.

Table 3. Diastereoselective esterification of ketenes prepared in situ.



Entry	Acyl chloride **2**	*dr*[a] (yield [%])[b] Z = O	Z = NBn
1[c]	 *rac*-**2a**	9:1 (86) (*R*,*R*)-**3a**	49:1 (88) (*R*,*R*)-**5a**
2[d]	 *rac*-**2b**	24:1 (88) (*R*,*R*)-**3b**	99:1 (86) (*R*,*R*)-**5b**
3[d]	 (*S*)-**2c**	49:1 (96) (*R*,*R*)-**3c**	>99:1[e] (91) (*R*,*R*)-**5c**
4[d]	 *rac*-**2d**	24:1 (82) (*R*,*R*)-**3d**	49:1 (75) (*R*,*R*)-**5d**
5[c,f]	 *rac*-**2e**	10:1 (78) (*R*,*R*)-**3e**	>99:1[e] (77) (*R*,*R*)-**5e**

[a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield based on **2**. [c] Et_3N was added to a solution containing **2** and (*R*)-pantolactone or (*R*)-*N*-benzylpantolactam at –10 °C. [d] Et_3N was added to a solution of **2** at –10 °C. After stirring the reaction mixture for 0.5 h, an (*R*)-pantolactone or (*R*)-*N*-benzylpantolactam solution was added dropwise to a mixture of **2** and Et_3N in toluene at –10 °C. [e] (*S*,*R*)-**5** was not detected by ^{1}H NMR spectroscopy. [f] THF was used as the solvent instead of toluene. Bn = benzyl.

(Scheme 3).[15] Thus, the reaction conditions promoting the dissociation of hydrogen bonds in the transition state (i.e., the use of a less basic, nucleophilic amine, alkoxide addition via an enolate, or a change in the polar solvent)[16] would lower the rotational barrier energy to promote equilibration of the two ketene acetals, thereby resulting in decreased selectivity. This hypothesis suggests that the low diastereoselectivity for ester (*R*,*R*)-**3a** protonated by the alcohol is due to weak hydrogen-bonding interactions because of the low electron density of the oxygen atoms in a ketene acetal with an electron-withdrawing sulfone moiety on the aryl ring.

To enhance significantly the hydrogen-bonding interactions of the oxygen atoms of the ketene acetal, we prepared (*R*)-*N*-benzylpantolactam, which has an amidic carbonyl moiety with a stronger proton affinity than (*R*)-pantolactone, as a chiral auxiliary. This auxiliary gave the corresponding ester (*R*,*R*)-**5a** from *rac*-**2a** with 98:2 *dr* in 88% yield even at –10 °C (Table 3, Entry 1). This auxiliary also worked well for nonfunctionalized acyl chloride *rac*-**2b** and other functionalized acyl chlorides, (*S*)-**2c** prepared from naproxen, ring-fused *rac*-**2d**, and *rac*-**2e**, giving the corresponding esters (*R*,*R*)-**5b**–**5e** (Entries 2–5) with higher diastereoselectivities than those obtained from (*R*)-pantolactone. Furthermore, ester (*R*,*R*)-**5a** was hydrolyzed at –10 °C without epimerization/racemization with lithium peroxide to give (*R*)-**1a** with a 98:2 *er* in 95% yield.[17,18]

Conclusions

We have elucidated that Et_3N as base is a key for the highly diastereoselective formation of esters from the corresponding acyl chlorides with (*R*)-pantolactone via ketene-derived complexes. Furthermore, we have discovered that (*R*)-*N*-benzylpantolactam is a more effective chiral auxiliary for the asymmetric synthesis of α-arylpropionic acids.

Experimental Section

General Procedure for the Synthesis of Esters (*R*,*R*)-3 and (*R*,*R*)-5

Procedure a: $SOCl_2$ (1.3 equiv.) was added to a solution of carboxylic acid **1** and Et_3N or DMF (3 mol-%) in toluene at 40 °C. After stirring for 4 h, the reaction mixture was concentrated under vacuum. The residue, acyl chloride **2**, was dissolved in toluene. Et_3N (2.0 equiv.) was added to the solution, and the resulting mixture was stirred at –10 °C for 0.5 h. A solution of (*R*)-pantolactone (1.3 equiv.) or (*R*)-*N*-benzylpantolactam (1.0 equiv.) in toluene was added dropwise to the yellow solution at –10 °C over 20 min. After stirring at –10 °C for 2 h, citric acid and H_2O were added to the reaction solution. After warming to 25 °C, the resulting solution was separated. The organic layer was washed with 10% aq. NaCl, dried with $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel with EtOAc/*n*-hexane (1:3 → 3:2) to give ester (*R*,*R*)-**3** or (*R*,*R*)-**5**.

Procedure b: $SOCl_2$ (1.3 equiv.) was added to a solution of carboxylic acid **1** and Et_3N or DMF (3 mol-%) in toluene at 40 °C. After stirring for 4 h, the reaction mixture was concentrated under vacuum. The residue, acyl chloride **2**, and (*R*)-pantolactone (1.3 equiv.)

or (*R*)-*N*-benzylpantolactam (1.0 equiv.) were dissolved in toluene. Et_3N (2.0 equiv.) was added to the solution, and the resulting mixture was stirred at –10 °C for 2 h. Citric acid and H_2O were added to the reaction solution. After warming to 25 °C, the resulting solution was separated. The organic layer was washed with 10% aq. NaCl, dried with $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel with EtOAc/*n*-hexane (1:3 → 3:2) to give ester (*R*,*R*)-**3** or (*R*,*R*)-**5**.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of the products.

Acknowledgments

We are grateful to Prof. Dr. D. G. Blackmond for useful comments and suggestions during the initial research on this mechanism.

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[8] Changing the solvent to THF or MeCN decreased the selectivity of (*R*,*R*)-[D]**3a** (THF: 11:1 *dr*, 87% yield; MeCN: 5:1 *dr*, 51% yield).
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[12] Use of Me_3N·HCl or pyridine·HCl instead of Et_3N·HCl gave ester (*R*,*R*)-**3b** with lower selectivity (Me_3N·HCl: 19:1 *dr*, 24% yield; pyridine·HCl: 2.4:1 *dr*, 20% yield).
[13] Use of free Et_3N with NaH instead of Et_3N·HCl gave a mixture containing ester (*R*,*R*)-**3b** with a 1.2:1 *dr*.
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[16] Changing the solvent to THF slightly contributed to the selectivity of ester (*R*,*R*)-**3b** (49:1 *dr*, 86% yield); however, the use of polar CH_3CN significantly decreased its selectivity (6:1 *dr*, 89% yield).
[17] (*R*)-*N*-Benzylpantolactam was recovered from the reaction mixture by extraction with toluene under basic conditions [59% yield based on (*R*,*R*)-**5a**, unoptimized].
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Received: September 11, 2013
Published Online: October 9, 2013

