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Phase-Transfer Catalyzed Asymmetric Conjugate Additions of β-Ketoesters to Acetylenic Ketones

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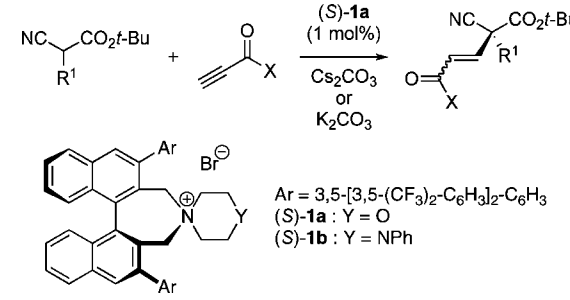
Abstract:

Asymmetric conjugate addition of cyclic β-keto esters to acetylenic ketones has been achieved with high enantioselectivity and moderate *E*/*Z* selectivity under the influence of a binaphthyl-modified 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl-substituted phase-transfer catalyst.

Introduction

Development of methods for stereoselective construction of quaternary stereocenters is one of the most important challenges in organic synthesis for efficient synthesis of complex natural products and drugs.[1] Asymmetric conjugate additions of carbon nucleophiles to α,β-unsaturated carbonyl systems constitute a useful carbon−carbon bond formation technique and have been used widely in asymmetric synthesis,[2] such as for generation of quaternary carbon centers in a stereoselective manner. A variety of different vinyl carbonyl compounds have been found useful for these conjugate addition reactions.[3] In contrast, there are only several reports dealing with the analogous conjugate addition reaction to the corresponding acetylenic acceptors.[4] An advantage of the conjugate addition to acetylenic acceptors is that the products obtained from the reaction possess a C═C double bond making them versatile building blocks for further transformation. Accordingly, we recently reported our case study on this subject by suitably designing certain chiral phase-transfer catalysts as promising organocatalysts.[5,6] Indeed, a new spiro-type phase-transfer catalyst (*S*)-**1a** has been designed for effecting a hitherto unknown asymmetric conjugate addition of α-alkyl-α-cyanoacetates to acetylenic esters[6a] and acetylenic ketones[6b] with high enantioselectivities (Scheme 1). This observation led us to examine the conjugate addition of β-keto esters to acetylenic ketones for construction of all-carbon quaternary stereocenters. Here, we report asymmetric conjugate additions of cyclic β-keto esters to acetylenic ketones under phase-transfer conditions.

Scheme 1



Results and Discussion

Attempted reaction of *tert*-butyl 2-oxocyclopentanecarboxylate **2a** and 3-butyn-2-one **3a** with K_2CO_3 (0.5 equiv) in the presence of a catalytic amount (1 mol %) of (*S*)-**1a** in toluene at 0 °C for 2 h gave rise to conjugate adducts **4aa** in 99% yield

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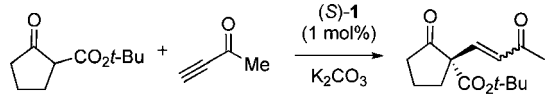
Table 1. **Catalytic enantioselective conjugate addition of *tert*-butyl 2-oxocyclopentanecarboxylate to 3-butyn-2-one[a]**

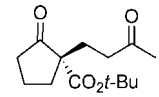


2a **3a** **4aa**

entry	catalyst	solvent	conditions	% yield[b] (*E*/*Z*)[c]	% ee[d]
1	(*S*)-**1a**	toluene	0 °C, 2 h	99 (3.1/1)	69/51
2	(*S*)-**1a**	*m*-xylene	0 °C, 1 h	99 (2.6/1)	76/57
3	(*S*)-**1a**	*o*-xylene	0 °C, 1 h	94 (3.4/1)	72/57
4	(*S*)-**1a**	CF_3−Ph	0 °C, 1 h	99 (2.4/1)	55/33
5	(*S*)-**1a**	THF	0 °C, 1 h	99 (1.5/1)	25/17
6	(*S*)-**1a**	*t*-BuOMe	0 °C, 1 h	99 (2.2/1)	77/67
7	(*S*)-**1a**	CPME[e]	0 °C, 1 h	99 (2.0/1)	76/65
8	(*S*)-**1a**	Et_2O	0 °C, 1 h	97 (1.5/1)	81/75
9	(*S*)-**1a**	Et_2O	−40 °C, 2.5 h	99 (1.7/1)	87/79
10	(*S*)-**1b**	Et_2O	−40 °C, 3 h	98 (1.2/1)	90/85
11[f]	(*S*)-**1b**	Et_2O	−40 °C, 8 h	99 (1.2/1)	91/84

[a] Unless otherwise specified, the reaction was carried out with 1.5 equiv of 3-butyn-2-one **3a** and 0.5 equiv of K_2CO_3 in the presence of 1 mol % of (*S*)-**1** under the given reaction conditions. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis. [e] CPME = Cyclopentyl methyl ether. [f] Use of 0.1 equiv of K_2CO_3.

with the *E*/*Z* ratio of 3.1:1. The enantiomeric excesses of (*E*)- and (*Z*)-**4aa** were found to be 69% and 51%, respectively, as shown in Table 1 (entry 1). The solvent effect was studied in detail as indicated for entries 2−8, and among several solvents, Et_2O gave the best results in terms of the enantioselectivity (entry 8). By using a lower temperature (−40 °C), the enantioselectivity was increased to 87% ee and 79% ee for (*E*)- and (*Z*)-**4aa,** respectively (entry 9). In contrast, the 1-phenylpiperazine-derived catalyst (*S*)-**1b** exhibited a slightly higher enantioselectivity (90% ee and 85% ee for (*E*)- and (*Z*)-**4aa,** respectively) than morpholine-derived catalyst (*S*)-**1a** (entry 10 vs 9). The amount of K_2CO_3 as a base could be reduced to even 0.1 equiv without any decrease of yield and enantioselectivity, though a prolonged reaction time was required (entry 11). The absolute configuration of the conjugate adducts, (*E*)-**4aa** and (*Z*)-**4aa** was firmly determined to be *S* by conversion to the known compound **5** with the catalytic hydrogenation (cat. Pd/C, H_2, MeOH).[7]



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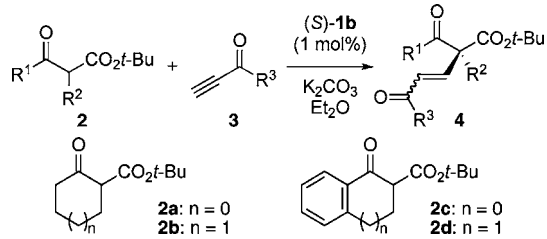
With the optimum reaction conditions determined, we further studied the generality of the asymmetric conjugate addition to various acetylenic ketones **3** using cyclic β-keto esters **2a**−**d** as nucleophiles, and some selected examples are listed in Table 2. Among cyclic β-keto esters, both five- and six-membered cyclic β-keto esters exhibited high enantioselection.[8] Acetylenic ketones **3** possessing *secondary*- and *tertiary*- as well as *primary*-alkyl groups also exhibited moderate to excellent enantioselectivities. Phenyl-substituted acetylenic ketone **3c** is also a viable substrate when aqueous 33% K_2CO_3 was used as a base in toluene (entries 3, 4, 8, and 10). In particular, the combination of *tert*-butyl indanonecarboxylate **2c** and acetylenic ketone **3b** (R^3 = *c*-Hex) gave rise to the highest enantioselectivity (entry 7). Although the current *E*/*Z* selectivity is only moderate,[9] an all-carbon quaternary stereocenter can be constructed in this asymmetric transformation, and the (*E*)- and (*Z*)-**4** products can be easily separated by simple column chromatography.

We are further exploring the applicability of these catalysts to related systems. For instance, the asymmetric conjugate addition of *tert*-butyl 2-oxocyclopentanecarboxylate **2a** to *tert*-butyl propiolate **6** with aqueous 33% K_2CO_3 in the presence of a catalyst (*S*)-**1b** in toluene at 0 °C for 20 h afforded the corresponding conjugate adduct **7** in 85% yield with good enantioselectivity (Scheme 2). Further results will be reported in due course.

Conclusions

Asymmetric conjugate addition of cyclic β-keto esters **2** to acetylenic ketones **3** has been achieved with high enantiose-

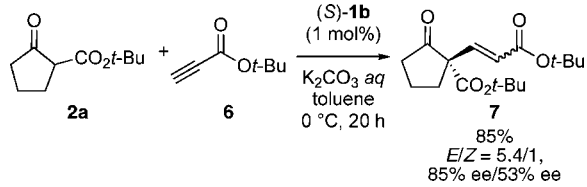
Table 2. **Catalytic enantioselective conjugate addition of cyclic β-keto esters to various acetylenic ketones[a]**



entry	**2**	**3** (R^3)	conditions	% yield[b] (*E*/*Z*)[c]	% ee[d]
1	**2a**	**3a** (R^3 = Me)	−40 °C, 3 h	98 (1.2/1); **4aa**	90/85
2	**2a**	**3b** (R^3 = *c*-Hex)	−40 °C, 2 h	99 (1.3/1); **4ab**	91/83
3[e]	**2a**	**3c** (R^3 = Ph)	−20 °C, 1 h	95 (2.3/1); **4ac**	90/60
4[e]	**2b**	**3c** (R^3 = Ph)	−20 °C, 24 h	65 (2.0/1); **4bc**	84/61
5[f]	**2b**	**3d** (R^3 = *t*-Bu)	−40 °C, 40 h	90 (1/2.0); **4bd**	77/84
6	**2c**	**3a** (R^3 = Me)	−40 °C, 1.5 h	99 (1/1.1); **4ca**	81/62
7	**2c**	**3b** (R^3 = *c*-Hex)	−40 °C, 2 h	99 (1/5.5); **4cb**	93/85
8[e]	**2c**	**3c** (R^3 = Ph)	−20 °C, 1 h	99 (2.0/1); **4cc**	82/56
9	**2c**	**3d** (R^3 = *t*-Bu)	−40 °C, 2 h	99 (1/3.6); **4cd**	83/79
10[e]	**2d**	**3c** (R^3 = Ph)	−20 °C, 2 h	90 (2.0/1); **4dc**	85/81
11	**2d**	**3d** (R^3 = *t*-Bu)	−40 °C, 24 h	68 (3.2/1); **4dd**	85/74

[a] Unless otherwise specified, the reaction was carried out with 1.0 equiv of cyclic β-keto ester **2**, 1.5 equiv of acetylenic ketone **3** and 0.5 equiv of K_2CO_3 in the presence of 1 mol % of (*S*)-**1b** under the given reaction conditions. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis. [e] Use of aqueous 33% K_2CO_3 and toluene as a solvent. [f] Use of 1.2 equiv of Cs_2CO_3.

Scheme 2



lectivity and moderate *E*/*Z* selectivity under the influence of a binaphthyl-modified 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl-substituted phase-transfer catalyst **1b**. The products should prove to be useful synthetic intermediates as much as otherwise difficult to prepare all-carbon quaternary stereocenters.[10]

Experimental Section

A Typical Experimental Procedure of Catalytic Enantioselective Conjugate Addition. β-Keto ester **2a** (55 mg, 0.30 mmol) and chiral ammonium salt (*S*)-**1b** (4.6 mg, 0.0030 mmol, 1 mol %) in Et_2O (3.0 mL) under Ar were treated with 3-butyn-2-one **3a** (35 μL, 0.45 mmol, 1.5 equiv). After the reaction system was cooled to −40 °C, K_2CO_3 (21 mg, 0.15 mmol, 0.50 equiv) was added in a single portion. The reaction mixture was stirred vigorously at −40 °C for 3 h, quenched with saturated aqueous NH_4Cl (10 mL), extracted with Et_2O (10 mL), dried over Na_2SO_4, and concentrated. The *E*/*Z* ratio was determined to be 1.2:1 by ^{1}H NMR analysis of the crude sample. Separation by column chromatography on silica gel with hexane/ethyl acetate (8:1−4:1) afforded (*E*)-**4aa** and (*Z*)-**4aa** in 98% combined yield. The enantiomeric excess of these (*E*)-**4aa** and (*Z*)-**4aa** was determined by chiral HPLC analysis [(*E*)-**4aa**: DAICEL CHIRALPAC AS-H, isopropanol/hexane = 1:10, flow rate = 0.5 mL/min, λ = 220 nm, retention time: 19.4 min (minor) and 25.4 min (major); (*Z*)-**4aa**: DAICEL CHIRALCEL OD-H, isopropanol/hexane = 1:10, flow rate = 0.5 mL/min, λ = 220 nm, retention time: 10.2 min (minor) and 11.6 min (major)].

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(8) Acyclic β-keto esters as nucleophiles showed moderate reactivity and enantioselectivity (~40% ee).

(9) The *Z* isomer of compound **4ac** could isomerize to the corresponding *E* isomer without loss of enantioselectivity, see: Poulsen, T. B.; Bernardi, L.; Bell, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6551.

(10) Asymmetric phase-transfer reactions on a large scale, see: (a) Patterson, D. E.; Xie, S.; Jones, L. A.; Osterhout, M. H.; Henry, C. G.; Roper, T. D. *Org. Process Res. Dev.* **2007**, *11*, 624. (b) Wang, Y.-G.; Maruoka, K. *Org. Process Res. Dev.* **2007**, *11*, 628. (c) Scott, J. P.; Ashwood, M. S.; Brands, K. M. J.; Brewer, S. E.; Cowden, C. J.; Dolling, U.-H.; Emerson, K. M.; Gibb, A. D.; Goodyear, A.; Oliver, S. F.; Stewart, G. W.; Wallace, D. J. *Org. Process Res. Dev.* **2008**, *12*, 723.