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Phase-Transfer-Catalyzed Olefin Isomerization/α-Alkylation of α-Alkynylcrotonates as a Route for 1,4-Enynes

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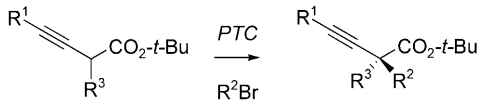
Abstract: The phase-transfer-catalyzed alkylation of α-alkynylcrotonates was developed as a means to provide 1,4-enynes deconjugated by an all-carbon quaternary center. Extension to the asymmetric version using the chiral phase-transfer catalyst (*S*)-**3** provided the alkylated compounds with up to 87% *ee*.

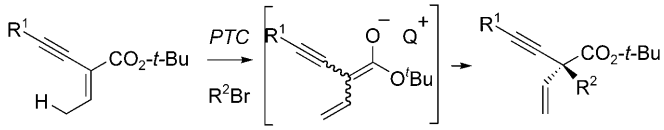
Keywords: acetylenes; alkylation; asymmetric synthesis; enynes; phase-transfer catalysis

Construction of the asymmetric all-carbon quaternary center has widely attracted the attention of synthetic community as it could only be achieved by relying on the use of an enantioselective C–C bond-forming process.[1] Among the variety of protocols developed to date, phase-transfer-catalyzed asymmetric functionalization has been increasingly accepted as one promising tool for this purpose.[2] In this context, we recently introduced the phase-transfer-catalyzed enantioselective alkylation of α-alkynyl esters [Scheme 1, Eq. (1)] as a novel means to generate an asymmetric all-carbon quaternary center bearing an acetylene moiety which is hardly accessible by other means.[3]

Eq. (1): α-alkylation (previous work)



Eq. (2): olefin-isomerization/α-alkylation (**this work**)



Scheme 1. Phase-transfer-catalyzed olefin isomerisation/α-alkylation sequence.

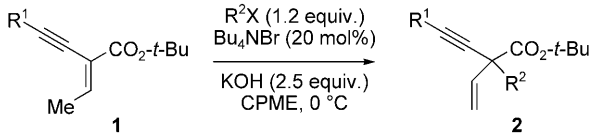
As an extension of this method, we became interested in implementation of the base-mediated olefin isomerization/α-alkylation of α-alkynylcrotonates, generating 1,4-enynes with an all-carbon quaternary center as a linch-pin [Scheme 1, Eq. (2)].[4] It is anticipated that incorporation of a vinyl moiety to the product would increase the synthetic value of this process, given its unrivaled diversity of synthetic transformations and functional orthogonality with alkynes, as well as a myriad of reactions utilizing 1,n-enynes as substrates.[5]

Although the olefin isomerization/alkylation reactions of α-alkylcrotonoyl esters are well known in the literature,[6] they normally required the use of strong base under an inert atmosphere. In contrast, the reaction system developed herein can be accomplished under operationally simple phase-transfer catalytic conditions owing to the electron-withdrawing property of the α-alkynyl group which facilitates the enolate formation.

The scarcity of the methodologies to access 1,4-enynes connected by an all-carbon quaternary center in the literature,[7,8] despite their synthetic potential, initially prompted us to establish the reliability of our synthetic plan in the synthesis of racemic materials **2** using α-silylethynylcrotonate (**1**, R^1 = TBS) as substrate (Table 1). After brief screening of the base and solvent, we settled on the use of cyclopentyl methyl ether (CPME) as solvent and powdered KOH as base to promote the process.

The olefin isomerization/alkylation of α-silylethynylcrotonate and benzylic bromides could be facilitated irrespective of the substituent on the benzene ring (Table 1, entries 1–4). In the case of sterically demanding alkyl bromides like 2-chlorobenzyl bromide (entry 3), a small amount of the γ-alkylated compound was observed. Use of allyl and propargyl bromides offered a facile access to a densely functional-

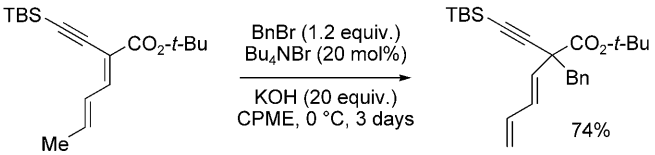
Table 1. Synthesis of racemic 1,4-enynes.[a]



Entry	R^1	R^2X	Time [h]	Yield [%][b]
1	TBS	BnBr	6	85
2		3-$MeC_6H_4CH_2Br$	24	94
3		2-$ClC_6H_4CH_2Br$	8	72
4		4-$MeOC_6H_4CH_2Br$	6	91
5		$H_2C{=}CHCH_2Br$	22	89
6		$HC{\equiv}CCH_2Br$	12	88
7[c]		MeI	22	57
8[c]		EtI	41	53
9	Ph	BnBr	11	92
10[d]	*n*-Bu	BnBr	12	56

[a] Reactions were performed with α-alkynylcrotonate (0.10 mmol) and alkyl halide (0.12 mmol) in the presence of 20 mol% Bu_4NBr (0.02 mmol) and powdered KOH (0.25 mmol).
[b] Isolated yield.
[c] Performed with 5 equiv. of alkyl halide (0.50 mmol) and 10 equiv. of powdered KOH (1.0 mmol).
[d] Performed with $CsOH{\cdot}H_2O$ (1.0 mmol).

ized dienyne and endiyne (entries 5 and 6). Methylation and ethylation could be achieved as well by using excess amounts of the corresponding alkyl iodides (5 equiv.) and powdered KOH (10 equiv.), giving the 1,4-enynes in moderate yields (entries 7 and 8). The reaction system was then applied to other α-alkynylcrotonates bearing a different functionality at the acetylene terminus. Whereas the α-phenylethynylcrotonate could be utilized uneventfully (entry 9), use of the substrate bearing an alkyl moiety was found to be sluggish. Accordingly, cesium hydroxide was used as a stronger base to give the 1,4-enyne in a reasonable yield (entry 10).

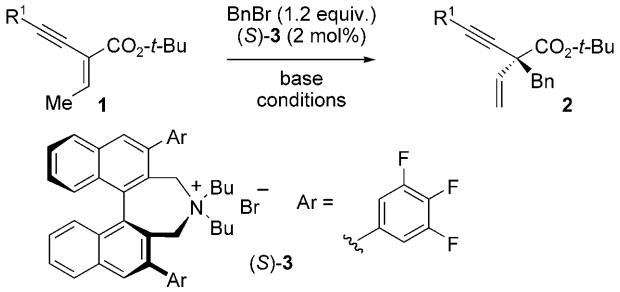


Scheme 2. Phase-transfer-catalyzed alkylation of the hexa-2,4-dienoate.

In addition, the established reaction conditions could be extended to the alkylation of the hexa-2,4-dienoate by use of a large excess of potassium hydroxide to give the product with a diene moiety (Scheme 2).[9]

As the viability of our synthetic plan for the preparation of 1,4-enynes connected by an all-carbon quaternary center was validated, we then moved our attention to implement the asymmetric version of this reaction using chiral quaternary ammonium salt as catalyst (Table 2). In the initial investigation, the binaphthyl-modified phase-transfer catalyst (*S*)-**3** was selected as an appropriate catalyst in consideration of

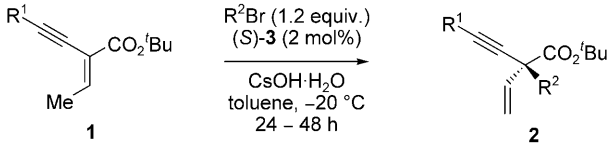
Table 2. Screening of the reaction conditions.



Entry	R^1	Base	Solvent	Temp./time [°C/h]	Yield [%][b]	*ee* [%][c]
1	TBS	KOH	CPME	0/20	70	20
2	TPS	KOH	CPME	0/33	70	29
3	TMS	KOH	CPME	0/32	66	42
4	Ph	KOH	CPME	0/48	93	81
5		KOH	toluene	0/48	53	82
6		KOH	toluene	−20/48	trace	-
7		$CsOH{\cdot}H_2O$	toluene	0/21	97	82
8		$CsOH{\cdot}H_2O$	toluene	−20/24	89	87

[a] Reactions were performed with α-alkynylcrotonate (0.10 mmol) and benzyl bromide (0.12 mmol) in the presence of 2 mol% (*S*)-**3** (0.002 mmol) and powdered KOH (0.25 mmol) or $CsOH{\cdot}H_2O$ (0.50 mmol).
[b] Isolated yield.
[c] Determined by chiral HPLC.

Table 3. Phase-transfer catalyzed asymmetric olefin isomerisation/α-alkylation.[a]



Entry	R^1	R^2	Yield [%][b]	*ee* [%][c]
1	Ph	Bn	89	87
2		3-$MeC_6H_4CH_2$	80	82
3		2-$ClC_6H_4CH_2$	85	80
4		4-$MeOC_6H_4CH_2$	78	76
5		$H_2C{=}C(CH_3)CH_2$	82	87
6		$(CH_3)_2C{=}CHCH_2$	91	64
7		$HC{\equiv}CCH_2$	67	75
8	4-ClC_6H_4	Bn	69	83
9	4-$MeOC_6H_4$	Bn	83	58

[a] Reactions were performed with α-alkynylcrotonate (0.10 mmol) and alkyl halide (0.12 mmol) in the presence of 2 mol% (*S*)-**3** (0.002 mmol) and powdered $CsOH{\cdot}H_2O$ (0.50 mmol).
[b] Isolated yield.
[c] Determined by chiral HPLC.

our previous study, and the reaction was carried out under otherwise identical reaction conditions as above. Use of α-silylethynylcrotonates led to disappointingly low enantioselectivities, irrespective of the substituents of the silyl group (entries 1–3). On the other hand, use of α-phenylethynylcrotonate was found to be promising, giving the alkylated compound with 81% *ee* (entry 4). Optimization of the reaction conditions revealed a slight increase of the enantioselectivity by use of toluene as solvent (entry 5) and a significant decrease of the reaction rate when conducted at −20 °C (entry 6). As the use of cesium hydroxide successfully increased the reaction rate without deteriorating the enantioselectivity (entry 7), the reaction was then carried out at −20 °C using cesium hydroxide. As such, the *ee* could be further improved to 87% *ee* (entry 8).[10] Although some other catalysts were also screened under these reaction conditions, none of them exceeded the result attained by use of (*S*)-**3**.[11]

With the optimized conditions in hand, we investigated the scope of this asymmetric transformation using α-arylethynylcrotonates and alkyl halides (Table 3). As for the benzylic bromides, the reaction provided the alkylated compounds consistently with nearly 80% *ee* (entries 2–4). On the other hand, the enantioselectivities varied considerably when allylic bromides were used. Whereas the alkylation with methallyl bromide resulted in good enantioselectivity, use of prenyl bromide furnished the alkylated compound with 64% *ee* (entries 5 and 6). Propargylation could be also accomplished with modest selectivity (entry 7). Attachment of an electron-withdrawing group at the aryl moiety of the alkyne terminus was tolerated, giving the product in 69% yield with 83% *ee* (entry 8). In contrast, use of the substrate with an electron-donating group led to a significant drop of the *ee* value (entry 9).

In conclusion, we developed herein the operationally simple procedure for the synthesis of 1,4-enynes linked by an all-carbon quaternary center. Investigations toward the asymmetric variant led to the observation that α-arylethynylcrotonates could be utilized to give 1,4-enynes with a promising level of enantioselectivities.

Experimental Section

Representative Procedure for Asymmetric Alkylation of α-Alkynylcrotonate (Table 3, entry 1)

To a test tube equipped with the magnetic stir bar were added the catalyst (*S*)-**3** (0.002 mmol, 1.5 mg), toluene (0.50 mL), *tert*-butyl 2-(phenylethynyl)but-2-enoate (0.10 mmol, 24.2 mg) and benzyl bromide (0.12 mmol, 14.3 μL). After cooling the mixture to −20 °C, $CsOH{\cdot}H_2O$ (0.50 mmol, 93.3 mg) was added in one portion. The reaction was stirred vigorously at the same temperature for 24 h and quenched with saturated aqueous NH_4Cl. The organic layer was extracted with hexane, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluting with hexane/CH_2Cl_2/Et_2O = 200:20:3) to give the alkylated compound as a colorless oil; yield: 29.7 mg (89%).

Acknowledgements

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[10] For the determination of the absolute configuration, see Supporting Information.

[11] For details, see Supporting Information.

