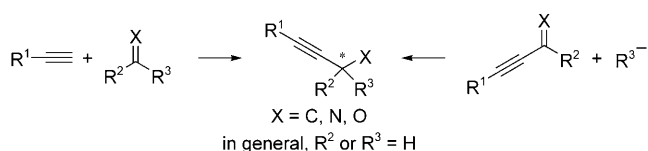


α -Chiral Acetylenes Having an All-Carbon Quaternary Center: Phase Transfer Catalyzed Enantioselective α Alkylation of α -Alkyl- α -alkynyl Esters**

Takuya Hashimoto, Kazuki Sakata, and Keiji Maruoka*

Owing to the synthetic versatility and modularity of acetylenes, chiral building blocks bearing acetylene moieties are widely used as valuable intermediates.^[1] Accordingly, tremendous efforts have been devoted to the development of catalytic asymmetric approaches to enable facile access to these attractive materials. The asymmetric transition metal mediated addition of terminal acetylenes (asymmetric alkynylations) to various prochiral electrophiles (Scheme 1, left),^[2] such as aldehydes,^[3] ketones,^[4] aldimines,^[5] and

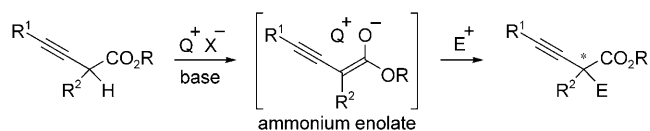


Scheme 1. Common tactics for the catalytic asymmetric synthesis of α -chiral acetylenes.

electron-deficient alkenes,^[6] as well as asymmetric additions to prochiral alkynyl substrates (Scheme 1, right),^[7–11] have been successfully adopted for this purpose.^[12,13]

However, most of these procedures are only applicable to the synthesis of α -chiral acetylenes having one hydrogen atom at the α position.^[14] We envisaged that asymmetric α functionalization of racemic α -alkyl- α -alkynyl esters via prochiral α -alkynyl enolates would offer a distinctive solution in this realm, providing α -chiral acetylenes having a quaternary stereogenic center (Scheme 2). The asymmetric C–C bond formation with these substrates is highly appealing since it is expected to generate an enantioenriched all-carbon quaternary center having both an appended acetylene and ester as useful functionalities;^[15] such a substrate is hardly accessible by use of the existing catalytic asymmetric methods.

As a suitable benchmark catalytic system to evaluate the viability of such a transformation, we selected phase transfer

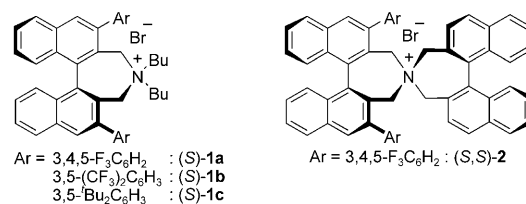
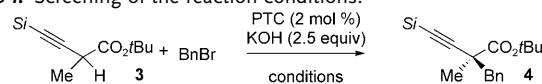


Scheme 2. Phase transfer catalyzed asymmetric functionalization of α -alkyl- α -alkynyl esters. Q = ammonium.

catalyzed asymmetric alkylation, taking advantage of its well-established practicality in analogous transformations, as well as our broad interest in phase-transfer catalysis.^[16]

The starting materials, α -alkyl- α -alkynyl esters, could be synthesized from α -iodoalkanoates and monosubstituted acetylenes by using the protocol reported by Oshima and co-workers.^[17] In an exploratory study, the asymmetric benzylation of the α -silyl ethynyl esters **3** was investigated under conventional phase transfer catalyzed alkylation reaction conditions using (S)-**1a** as the catalyst (Table 1).^[18] To our delight, the reaction of α -(*tert*-butyldimethylsilyl)ethynyl ester cleanly provided the desired compound in 87% yield with 63% *ee* (Table 1, entry 1). Examination of the steric

Table 1: Screening of the reaction conditions.^[a]



Entry	Cat.	Si	Solvent	T [°C], t [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	1a	TBS	toluene	0, 5	87	63
2	1a	TIPS	toluene	0, 20	92	18
3	1a	TMS	toluene	0, 2	68	78
4	1b	TMS	toluene	0, 2	62	74
5	1c	TMS	toluene	0, 2	48	11
6	2	TMS	toluene	0, 5	49	14
7	1a	TMS	mesitylene	0, 5	78	83
8	1a	TMS	mesitylene	–20, 12	70	86

[a] Reactions conditions: **3** (0.10 mmol) and benzyl bromide (0.12 mmol) in the presence of 2 mol% phase-transfer catalyst (0.002 mmol) and powdered KOH (0.25 mmol). [b] Yield of isolated product. [c] Determined by chiral HPLC analysis after desilylation of the product. TBS = *tert*-butyldimethylsilyl. TIPS = triisopropylsilyl, TMS = trimethylsilyl.

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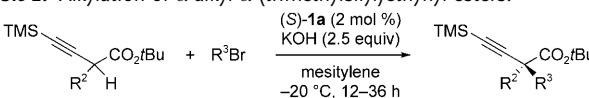
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effect of the silyl moiety revealed that the use of the bulky triisopropylsilyl group reduced the enantioselectivity to 18% *ee* (Table 1, entry 2), whereas the small trimethylsilyl-substituted ester was converted into the desired product with a promising level of asymmetric induction (Table 1, entry 3). Although the screening of other catalysts could not improve the selectivity (Table 1, entries 4–6), use of mesitylene as a solvent at lower temperature had a positive effect, furnishing the target material with 86% *ee* (Table 1, entries 7 and 8).

Having the optimized conditions in hand, the scope of this alkylation was then examined (Table 2). Irrespective of the electronic nature and substituent pattern of the benzylic

Table 2: Alkylation of α -alkyl- α -(trimethylsilyl)ethynyl esters.^[a]

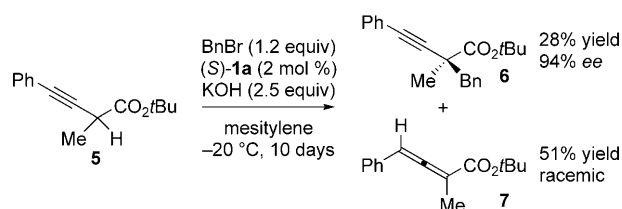


Entry	R ²	R ³	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	Me	Bn	70	86
2	Me	3-MeC ₆ H ₄ CH ₂	72	90
3	Me	4-MeOC ₆ H ₄ CH ₂	74	82
4	Me	2-ClC ₆ H ₄ CH ₂	79	83
5	Me	H ₂ C=C(CH ₃)CH ₂	59	90
6	Me	(CH ₃) ₂ C=CHCH ₂	89	87
7	Me	(<i>E</i>)-PhCH=CHCH ₂	73	84
8	Et	Bn	85	89
9	Et	2-MeC ₆ H ₄ CH ₂	81	87
10	Et	(<i>E</i>)-PhCH=CHCH ₂	78	90

[a] Reactions conditions: the alkynyl ester (0.10 mmol) and alkyl halide (0.12 mmol) in the presence of 2 mol% (*S*)-**1a** (0.002 mmol) and powdered KOH (0.25 mmol). [b] Yield of the isolated product. [c] Determined by chiral HPLC or GC analysis after desilylation of the product. Bn = benzyl.

halides, the alkylation gave the products in good yields and *ee* values (Table 2, entries 2–4).^[19] Excellent levels of enantioselectivity were attained in the reactions involving prenyl and methallyl bromides (Table 2, entries 5 and 6). Cinnamyl bromide could be utilized as well (Table 2, entry 7). To investigate the tolerance of the other α -alkyl group of the ester, α -ethyl- α -(trimethylsilyl)ethynyl ester was subjected to this enantioselective alkylation and resulted in the formation of the desired compounds in satisfactory yields and having *ee* values ranging from 87% to 90% (Table 2, entries 8–10).

In the process of expanding the substrate scope of this phase transfer catalyzed alkylation to include other α -alkynyl esters having either an aryl, alkenyl, or alkyl substituent at the acetylene terminus, we became aware of the significantly decreased reactivity of these substrates. For example, benzylation of the α -phenylethynyl ester **5** under the aforementioned reaction conditions led to the formation of product **6** in only 28% yield after 10 days, even though the enantioselectivity was remarkably high (Scheme 3). Examination of the remaining components revealed the complete disappearance of the starting α -alkynyl ester **5** and the formation of the allenyl ester **7** in a racemic form. This fact indicated the facile base-mediated isomerization of the α -alkynyl ester, which has a rather acidic α -hydrogen atom relative to the poorly acidic

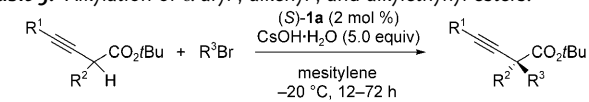


Scheme 3: Alkylation of α -methyl- α -phenylethynyl ester.

γ -hydrogen atom of the allenyl ester, thereby making the generation of the reactive enolate far less feasible.^[20] Notably, under our catalytic reaction conditions, the γ -alkylated allenyl ester was not observed at all.

At this point, we turned our attention to the use of cesium hydroxide monohydrate, as a stronger base to overcome this deficiency, under otherwise identical reaction conditions. As a result, the alkylated compound could be obtained in 88% yield within 27 hours without the loss of the enantioselectivity (Table 3, entry 1).^[21] This newly developed set of reaction conditions had a broad substrate scope with respect to alkyl

Table 3: Alkylation of α -aryl-, alkenyl-, and alkylethynyl esters.^[a]



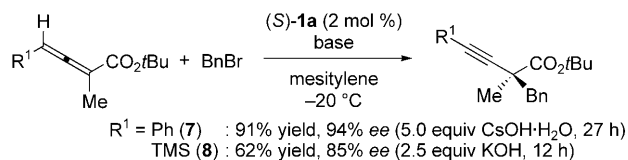
Entry	R ¹	R ²	R ³	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	Ph	Me	Bn	88	94
2	Ph	Me	3-MeC ₆ H ₄ CH ₂	85	94
3	Ph	Me	4-MeOC ₆ H ₄ CH ₂	81	90
4	Ph	Me	2-ClC ₆ H ₄ CH ₂	88	92
5	Ph	Me	H ₂ C=C(CH ₃)CH ₂	92	96
6	Ph	Me	H ₂ C=CHCH ₂	81	90
7	Ph	Me	HC≡CCH ₂	84	90
8 ^[d]	Ph	Me	<i>t</i> BuO ₂ CCH ₂	90	82
9	Ph	Et	Bn	88	93
10	Ph	Et	H ₂ C=C(CH ₃)CH ₂	87	95
11	4-MeOC ₆ H ₄	Me	Bn	92	94
12	4-MeOC ₆ H ₄	Me	H ₂ C=C(CH ₃)CH ₂	87	95
13	4-ClC ₆ H ₄	Me	Bn	85	96
14 ^[e]		Me	Bn	82	93
15 ^[e]	<i>n</i> Bu	Me	Bn	69	90

[a] Reactions conditions: the alkynyl ester (0.10 mmol) and alkyl halide (0.12 mmol) in the presence of 2 mol% (*S*)-**1a** (0.002 mmol) and powdered CsOH·H₂O (0.50 mmol). [b] Yield of the isolated product. [c] Determined by chiral HPLC analysis. [d] Performed at −30 °C. [e] 10 equiv of CsOH·H₂O.

halides and α -alkyl- α -alkynyl esters as showcased in Table 3. Use of benzylic and allylic halides in the reaction with α -methyl- α -phenylethynyl ester furnished the corresponding products in high yields and with enantioselectivities ranging from 90 to 96% *ee* (Table 3, entries 1–7). Alkylation with bromoacetate gave the product with slightly lower enantioselectivity (Table 3, entry 8). Alkylation of other α -aryl-ethynyl esters with different steric and electronic properties also worked very efficiently (Table 3, entries 9–13). Furthermore, this method was applicable to alkynyl esters having an

alkyl or an allenyl moiety at the acetylene terminus (Table 3, entries 14 and 15).

To investigate further the appearance of the allenyl ester in this reaction system, phase transfer catalyzed alkylation of the separately synthesized allenyl esters was implemented as shown in Scheme 4. As expected, alkylation of the γ -phenyl-allenyl ester **7**^[22] proceeded by using cesium hydroxide



Scheme 4. Phase transfer catalyzed enantioselective alkylation of allenyl esters.

monohydrate and the result was comparable to that of the ethynyl ester, whereas the reaction of γ -(trimethylsilyl)allenyl ester **8**^[23] only required the use of potassium hydroxide. This finding led us to conclude that the reactivity difference between α -silylethynyl esters and other α -alkynyl esters stems from the facile γ deprotonation of γ -silylallenyl esters generated in situ, which results from the stabilization of the α anion by the silyl moiety.^[24]

In summary, we demonstrated the feasibility of α -alkyl- α -alkynyl esters to undergo highly enantioselective α alkylation under phase-transfer reaction conditions, furnishing α -chiral acetylenes having an all-carbon quaternary center. A detailed investigation of this reaction system revealed the formation of an allenyl ester prior to the alkylation. Considering the increase in the number of various asymmetric catalysis reactions which rely on the in situ deprotonation of α -hydrogen atoms on the esters, the protocol reported herein will have broad applicability beyond phase-transfer catalysis as a means to afford an array of α -chiral acetylenes having a quaternary stereogenic center.

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