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Published on Web 12/22/2006

Organocatalytic Asymmetric Direct α-Alkynylation of Cyclic β-Ketoesters

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Abstract: The first organocatalytic enantioselective direct α-alkynylation of β-ketoesters and 3-acyl oxindoles is described. It is demonstrated that activated β-halo-alkynes undergo nucleophilic acetylenic substitution catalyzed by chiral phase-transfer compounds to afford the alkynylated products in high yields and excellent enantioselectivities. The potential of the reaction is first demonstrated for various alkynylating reagents having chloride and bromide as the leaving groups and substituents such as allyl and alkyl esters, amides, ketones, and sulfones. These reactions proceed with 74−99% yield and 88−97% ee. Then the scope in nucleophile is demonstrated for a large number of cyclic β-ketoesters with various ring-sizes and for oxindoles as well. The corresponding optically active products are formed in high yields and with enantioselectivities up to 98% ee. The procedure allows for the stereocontrolled attachment of an ethynyl unit in the α-position to the carbonyl compound by facile removal of the activating group, and this has been demonstrated for a number of the optically active allyl esters. Furthermore, the synthesis of optically active 1,4-enynes is also shown. The isolation and characterization by X-ray analysis of the catalyst with *p*-nitrophenolate as the counterion allowed us to propose a model of the catalyst−substrate intermediate which might account for the observed enantioselectivity of the organocatalytic enantioselective α-alkynylation reaction. Furthermore, it is suggested that this intermediate is also the reactive species for a number of other electrophiles adding to β-ketoesters giving enantioselectivities in the range of 90−98% ee.

Introduction

Since the discovery of ethyne by Edmund Davy in 1836 the carbon−carbon triple bond has fascinated chemists. The linear geometry and the electronic properties associated with the sp-hybridized carbon atoms, give alkynes a unique chemical reactivity that has been exploited for numerous transformations in organic chemistry.[1] In recent times, the interest in alkynes has expanded beyond organic chemistry to also include, for example, chemical biology, organometallic chemistry, material science, and nanoscience. In the field of organic chemistry, a recent example of a reaction involving the carbon−carbon triple bond with applications in growing scientific areas such as nanoscience and chemical biology[2] is the copper-catalyzed cycloaddition of azides to acetylenes pioneered by the groups of Sharpless[3a] and Meldal.[3b]

Chiral molecules containing a carbon−carbon triple bond with an adjacent stereogenic carbon-atom (propargylic stereocenter) have found great use both as optically active building blocks in the synthesis of natural products[4] and as bioactive compounds possessing antiviral properties.[5] Therefore, the efficient asymmetric synthesis of propargylic stereocenters has attracted the attention of many chemists, and within the past few years, reaction protocols employing optically active catalysts have been disclosed by several groups.[6,7] Fundamental studies in this

(1) (a) *The Chemistry of the Carbon-Carbon Triple Bond;* Patai, S., Ed.; Wiley: New York, 1978; Part 1−2. (b) *Modern Acetylene Chemistry*; Stang, P. J.; Diederich, F., Eds.; VCH: Weinheim, Germany, 1995. (c) *Acetylene Chemistry*; Diederich, F.; Stang, P. J.; Tykwinski, R. R., Eds.; VCH: Weinheim, Germany, 2005.

(2) See, for example: (a) Speers, A. E.; Adam, G. C.; Cravatt, B. F. *J. Am. Chem. Soc.* **2003**, *125*, 4686. (b) Prescher, J. A.; Bertozzi, C. R. *Nat. Chem. Biol.* **2005**, *1*, 13. (c) Burley, G. A.; Gierlich, J.; Mofid, M. R.; Nir, H.; Tal, S.; Eichen, Y.; Carell, T. *J. Am. Chem. Soc.* **2006**, *128*, 1398. (d) Dichtel, W. R.; Miljanić, O. Š.; Spruell, J. M.; Heath, J. R.; Stoddart, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10388.

(3) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

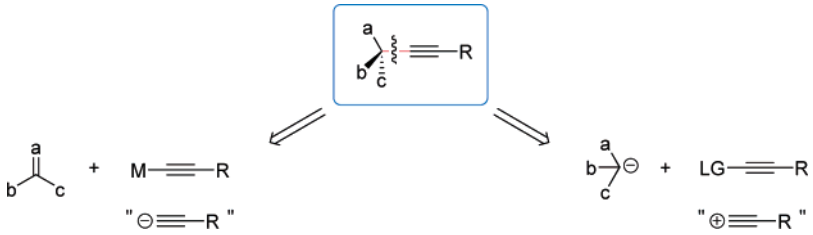
(4) See, for example: (a) Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 15196. (b) Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611.

(5) See, for example: (a) Jiang, B.; Si, Y.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 216. (b) Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Gearhart, L. A.; Magnus, N. A.; Bacheler, L. T.; Diamond, S.; Jeffrey, S.; Klabe, R. M.; Cordova, B. C.; Garber, S.; Logue, K.; Trainor, G. L.; Anderson, P. S.; Erickson-Viitanen, S. K. *J. Med. Chem.* **2000**, *43*, 2019.

(6) For additions to aldehydes catalytic in metal see: (a) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (b) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451. (c) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760. (d) Chen, Z.; Xiong, W.; Jiang, B. *Chem. Commun.* **2002**, 2098. For procedures stoichiometric in metal, see: (e) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (f) Trost, B. M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8. (g) Lui, L.; Wang, R.; Kang, Y.-F.; Cai, H.-Q.; Chen, C. *Synlett* **2006**, 1245. For additions to imines catalytic in metal see: (h) Wei, C; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. For procedures stoichiometric in metal, see ref 5a. For catalytic conjugate alkyne addition, see: (i) Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682. (j) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373. (k) Aschwanden, P.; Carreira, E. M. in *Acetylene Chemistry*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; VCH: Weinheim, Germany, 2005, Chapter 3, pp 101−138.

10.1021/ja067289q CCC: $37.00

Scheme 1. Two Methods for the Construction of Propargylic Stereocenters with Concomitant Formation of the C−C Bond[a]



[a] (Left) Addition of metal-acetylides to prochiral electrophiles; (right) acetylenic substitution by prochiral nucleophiles.

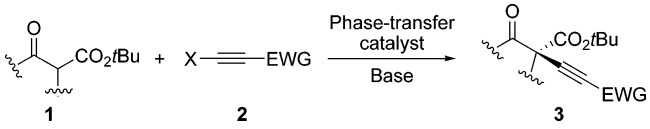
respect have been carried out by the group of Carreira.[6a,e,j] A common feature of the procedures published thus far is their reliance on the catalytic formation of optically active metal-acetylides which can add to a number of different prochiral electrophiles (Scheme 1, left). This approach has been successful in the addition of terminal alkynes to carbonyl compounds,[6a−g] imines,[6h,5a] and more recently to α,β-unsaturated carbonyl derivatives.[6i] Unfortunately, terminal alkynes equipped with electron-withdrawing groups (e.g., propiolates and propynones) have rarely been applied with success in these types of reactions owing to self-addition of the activated alkynes under the basic reaction conditions.[8]

An alternative approach to the formation of propargylic stereocenters can be envisioned by inverting the reactivity of the acetylenic system. For instance, triple bonds equipped with potential leaving groups, such as halides, can under suitable conditions substitute the leaving group for a carbanion nucleophile via an addition−elimination mechanism (Scheme 1, right).

Such acetylenic substitutions have been reported for several combinations of haloalkynes and both carbon- and heteroatom-centered nucleophiles,[9] and in the case of an enolate as the nucleophile, this reaction results in the α-alkynylation (assuming C-regioselectivity) of the corresponding carbonyl compound.

The α-alkynylation of enolates can also be realized through the use of hypervalent alkynyl−main-group derivatives such as alkynyl−iodonium salts,[10] or alternatively using in situ formed alkynyl−lead triacetate reagents.[11] Mechanistically, the former reaction has been shown to involve the formation of a carbene intermediate eventually rearranging to the α-alkynylated carbonyl compound, while the latter proceeds through formation of an enolate alkynyl−lead intermediate which collapses to afford the same product. It is worth mentioning, that enolate alkynylations of the latter type were recently applied by the group of Grossman in the racemic synthesis of the bicyclo-[3.3.1]nonane skeleton found in the polycyclic polyprenylated acylphloroglucinols.[12]

Scheme 2. Catalytic Enantioselective Acetylenic Substitution



Despite the synthetic utility of such enolate alkynylations, enantioselective variants of the different reactions outlined above have remained unexplored.[13] In this paper we wish to provide a contribution toward this goal, namely the development of organocatalytic enantioselective alkynylation of β-ketoesters through phase-transfer-catalyzed[14] acetylenic substitution (Scheme 2).

Results and Discussion

Electrophile Synthesis and Scope. It is important to mention some considerations related to the choice of the acetylenic electrophile. As shown below, it is possible to employ different haloalkynes in the reaction. We were, however, especially intrigued by the possibility of choosing one of the groups so that it could be "exchanged" with hydrogen in one easy chemical transformation—thereby enabling the attachment of an ethynyl unit in an enantioselective manner.

It became apparent to us, that compounds such as **2a**,**b** and **4** outlined in Figure 1 possessed these features. However, as alkyne **4** is a suspected carcinogen[15] and is known to form explosive mixtures with air,[13] we decided to focus our attention on allyl 3-halopropiolates **2a**,**b**.[16]

Traditionally, the synthesis of haloalkynes is performed through formation of a metal-acetylide followed by reaction with an electrophilic halogen-source. For instance, the reaction between an alkyne and *N*-bromosuccinimide (NBS) in the

(7) Asymmetric synthesis of propargylic stereocenters can also be achieved through the Nicholas reaction, for a review see: (a) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133. By asymmetric reduction of ynones (propargylic alcohols): (b) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938. By resolution of racemic propargylic alcohols: (c) Birman, V. B. M.; Guo, L. *Org. Lett.* **2006**, *8*, 4859 and references herein.

(8) For a discussion of this problem and an alternative solution, see: Tejedor, D.; García-Tellado, F.; Marrero-Tellado, J. J.; de Armas, P. *Chem.—Eur. J.* **2003**, *9*, 3122.

(9) For a review see: (a) Miller, S. I.; Dickstein, J. I. *Acc. Chem. Res.* **1976**, *9*, 358. (b) Dickstein, J. I.; Miller, S. I. in *The Chemistry of the Carbon−Carbon Triple Bond;* Patai, S., Ed.; Wiley: New York, 1978; Part 2 p 523.

(10) For reviews see: (a) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997. (b) Stang, P. J. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, Germany, 1995; Chapter 3, pp 67−98. (c) Stang, P. J. *Angew. Chem., Int. Ed.* **1992**, *31*, 274. See also: (d) Kitamura, T.; Nagata, K.; Taniguchi, H. *Tetrahedron Lett.* **1995**, *36*, 1081. (e) Bachi, M. D.; Bar-Ner, N.; Stang, P. J.; Williamson, B. L. *J. Org. Chem.* **1993**, *58*, 7923.

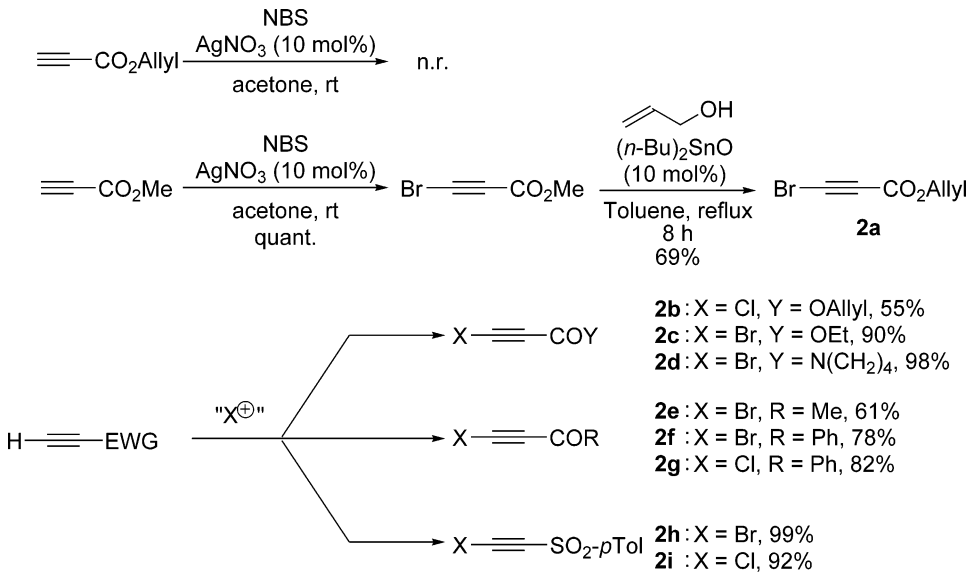
(11) See, for example: Moloney, M. G.; Pinhey, J. T.; Roche, E. G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 333.

(12) Ciochina, R.; Grossman, R. B. *Org. Lett.* **2003**, *5*, 4619.

(13) For racemic acetylenic substitutions involving enolates see: (a) Kende, A. S.; Fludzinski, P.; Hill, J. H.; Swenson, W.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 3551. (b) Jończyk, A.; Kuliński, T.; Czupryniak, M.; Balcerzak, P. *Synlett* **1991**, 639.

(14) For a review: (a) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 727. For recent examples of phase-transfer catalyzed asymmetric reactions, see: (b) Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2548. (c) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975. (d) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4564. (e) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139. (f) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3981. (g) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-k.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-s. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036. (h) Kita, T.; Georgieva, A.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2832. (i) Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622. (j) Fini, F.; Bernardi, L.; Herrera, R. P.; Pettersen, D.; Ricci, A.; Sgarzani, V. *Adv. Synth. Catal.* **2006**, *348*, 2043.

Scheme 3. Synthesis of Activated β-Haloalkynes **2a**−**i**[a]



[a] For details, see Supporting Information.

presence of catalytic amounts of $AgNO_3$ has been a popular method for the introduction of bromine.[17] To our surprise, this method failed for the synthesis of **2a** (Scheme 3, top).[18]

We therefore carried out the synthesis by dibutyltin(IV) oxide-catalyzed transesterification with allylic alcohol of the corresponding methyl ester (69% yield, Scheme 3, middle), which was easily prepared by the $AgNO_3$-catalyzed bromination mentioned above. Using similar chemistry, several other activated β-bromoalkynes **2c**−**f**,**h** having different activating groups were also prepared, whereas the synthesis of chloro-derivatives **2b**,**g** and **2i** required the use of *tert*-butyl hypochlorite as the halide-source and potassium *tert*-butoxide as the catalyst (Scheme 3, bottom).[19]

Having synthesized the different activated β-haloalkynes **2**, we surveyed their ability to act as alkynylating agents in a model reaction employing *tert*-butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **1a** as the nucleophile (eq 1, Table 1). The phase-transfer-catalyst system employed was recently developed by our group to effect enantioselective vinylic substitution reactions of β-ketoesters.[20] In this work, three parameters were identified to be critical for obtaining high enantioselectivities: (i) the β-ketoesters employed had to be equipped with bulky ester groups (e.g., *tert*-butyl), (ii) the reactions should be carried out in a liquid−liquid phase-transfer system, and (iii) the phase-transfer-catalysts (based on *N*-anthracenemethyl dihydrocinchonine **5a** or the quasienantiomer **5′a**, see Figure 2) had to be functionalized on the C9-hydroxyl group with sterically demanding substituents. This resulted in the preparation of the corresponding 1-adamantoyl derivatives (**5b** and **5′b**) which were found to afford the highest enantioselectivities.[20]

As demonstrated in Table 1, this catalyst system was found to be highly effective for the acetylenic substitution reaction. Attempts to modify the catalyst structure and/or the solvent system, resulted in lower enantioselectivities (see Supporting Information). It is possible to employ alkynes equipped with ester groups (entries 1, 2), amides (entry 3), ketones (entries 4, 5), and sulfones (entry 6), and in all cases we obtained the alkynylated β-ketoesters **3a**−**f** in good to high yields (62−99%) and with excellent stereoselectivities (generally >95% ee; for **3f**, 90% ee). The reactivity of the catalytic system was found to be easily fine-tuned through the choice of the aqueous base employed and the identity of the leaving group (Cl or Br). For instance, in the case of β-haloalkyne **2d** having an amide as the activating group (entry 3), the reaction was found to be sluggish when using aq K_2CO_3 (33%); however, the presence of a more concentrated base solution (50% Cs_2CO_3) resulted in complete consumption of the starting material within 24 h at −20 °C. The choice of the leaving group serves two purposes in this respect. Exchange of bromide for chloride generally results in a more reactive electrophile;[9b] however, it also effectively eliminates a possible side reaction of the system, namely, the attack of the nucleophile on the halide resulting in release of the terminal acetylene eventually resulting in additional side reactions (e.g., addition on the triple bond by the β-ketoester, see also mechanistic discussion later). Problems of this kind were encountered in the case of highly electron-deficient bromoalkynes **2f** and **2h** and in both cases the preparation of the corresponding chloride compounds **2g** and **2i** restored the "normal" reactivity.

Nucleophile Synthesis and Scope. As stated above, a bulky *tert*-butyl ester group in the β-dicarbonyl compounds was found to be requisite for obtaining good enantioselectivities in the substitution reactions catalyzed by the cinchonine and cinchonidine catalysts **5b** and **5′b**. Although the importance of this bulky ester moiety is in line with a number of different reports dealing with enantioselective transformations of cyclic β-ketoesters,[21]

(15) Green, T. *Hum. Ecol. Risk Assess.* **2001**, *7*, 677.
(16) The allyloxycarbonyl (alloc) group can be removed from an alkyne by palladium(0)-catalyzed deallylation−decarboxylation. See: (a) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; p 409. (b) Okamoto, S.; Ono, N.; Tani, K.; Yoshida, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1994**, 279.
(17) Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed.* **1984**, *23*, 727.
(18) Upon addition of $AgNO_3$ (10 mol%) to the reaction mixture in acetone we observed the immediate formation of a greyish precipitate. This precipitate is presumed to originate from a reaction between the silver(I) and allyl propiolate resulting in irreversible removal of catalyst from the catalytic cycle.
(19) Acheson, R. M.; Ansell, P. J.; Murray, J. R. *J. Chem. Res., Synop*. **1986**, 378.
(20) Poulsen, T. B.; Bernadi, L.; Bell, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6551.

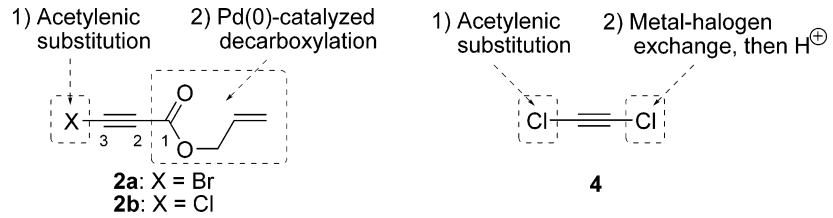


Figure 1. Two types of activated halo-alkynes enabling easy two-step attachment of an ethynyl unit by initial acetylenic substitution followed by removal of the other group.

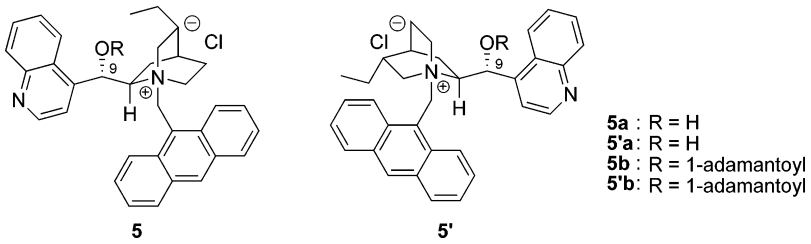


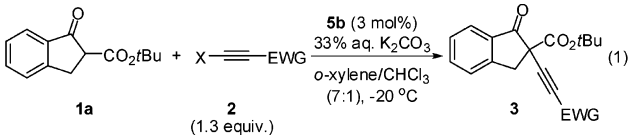
Figure 2. Structures of the dihydrocinchonine and dihydrocinchonidine derived catalysts **5** and **5′**.

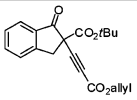
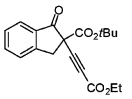
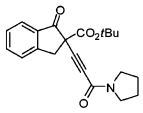
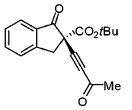
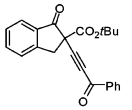
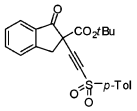
easy access to these compounds seems to be limited to indanone derivatives like **1a**−**d**, available through a transesterification reaction,[22] and to unsubstituted, non-ring-fused compounds like **1g** and **1h**, obtainable through a Dieckmann condensation.[23] However, we thought it would be of some interest to extend our enantioselective reaction also to substituted cyclohexenone derivatives, in light of the importance of these structures for target-oriented synthesis.[24] Considering the previously reported possibility of a regioselective C-acylation of cyclohexenones with methyl or allyl cyanoformate,[25] we tested the acylation of a few cyclohexenones with *tert*-butyl cyanoformate **6**[26] under similar conditions, giving the corresponding *tert*-butyl β-ketoesters **1i**−**k** in reasonable yields and complete C-regioselectivities (Scheme 4, top). The same reaction could also be used for the preparation of the 1-tetralone and 1-benzosuberone derivatives **1e** and **1f** (Scheme 4, bottom).

Although **1e** and **1f** were obtained only in rather low (unoptimized) yields, the easy availability in multigram quantities of the *tert*-butyl cyanoformate **6** and the difficult obtainment of **1e** and **1f** or structurally related *tert*-butyl β-ketoesters by other procedures,[27] render this approach useful for the preparation of these classes of compounds.

Having in our hands different *tert*-butyl β-ketoesters, we then explored their reactivity and their behavior in the catalytic enantioselective acetylenic substitution reaction. We focused on

Table 1. Catalytic Enantioselective Acetylenic Substitution—Scope of Alkynylating Agents.[a]

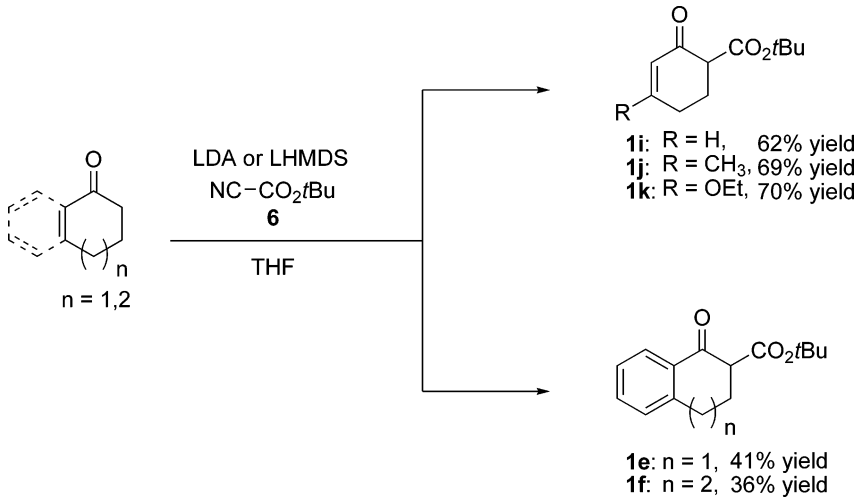


entry	electrophile	product	yield (%)[b]	ee (%)[c]
1	**2a**: X = Br		**3a** – 99 *ent*-**3a** – 97	96 88[d]
2	**2c**: X = Br		**3b** – 99	96
3[e]	**2d**: X = Br		**3c** – 96	96
4	**2e**: X = Br		**3d** – 88	(*S*)-95[f]
5	**2g**: X = Cl		**3e** – 90	97
6[g]	**2i**: X = Cl		**3f** – 74 (62)	80 (90)

[a] Reaction performed with 0.20 mmol of **1a** (0.15 M). [b] Isolated yield. [c] The enantiomeric excess was determined by HPLC using a chiral-stationary phase. [d] Reaction performed with the quasienantiomeric catalyst **5′b** derived from dihydrocinchonidine. [e] Reaction performed using Cs_2CO_3 (50%, aq) as the base and with the amide as the limiting reagent; yield based on the amide. [f] Absolute configuration determined by chemical correlation (see Supporting Information). [g] Reaction performed at 4 °C using chloroalkyne **2i**; in brackets is shown the result obtained using bromoalkyne **2h** at −20 °C.

(21) See for example: (a) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 947. (b) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240. (c) Hamashima, Y.; Yagi, K.; Takano, H.; Tamas, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530. (d) Sobhani, S.; Fielenbach, D.; Marigo, M.; Wabnitz, T.; Jørgensen, K. A. *Chem.—Eur. J.* **2005**, *11*, 5689. (e) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796. (f) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897.
(22) (a) Otera, J.; Yano, T.; Kawabata, T.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2383. (b) Nakajima, M.; Yamamoto, S.; Yamaguchi, Y.; Nakamura, S.; Hashimoto, S. *Tetrahedron* **2003**, *59*, 7307.
(23) Bunnage, M. E.; Davies, S. G.; Parkin, R. M.; Roberts, P. M.; Smith, A. D.; Withey, J. M. *Org. Biomol. Chem.* **2004**, *2*, 3337.
(24) For examples see: (a) Spassard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943. (b) Ursuda, H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2002**, *4*, 8591. (c) Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science* **2004**, *305*, 495. (d) Ho, T.-L. *Enantioselective Synthesis: Natural Products Synthesis from Chiral Terpenes*; Wiley: New York, 1992. (e) Klunder, A. J. H.; Zhu, J.; Zwanenburg, B. *Chem. Rev.* **1999**, *99*, 1163. See also ref 12.
(25) (a) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924.
(26) Carpino, L. A. *J. Am. Chem. Soc.* **1960**, *82*, 2725.

Scheme 4. Preparation of *tert*-Butyl β-Ketoesters through Acylation with *tert*-Butyl Cyanoformate **6**



the use of chloro and bromo alkynes **2a** and **2b**, since the possible removal of the allyl ester moiety through a Pd(0)-catalyzed deallylation−decarboxylation reaction (see below) can provide an easy access to the corresponding derivatives bearing a simple acetylenic unit, available for further chemical manipulations. As shown in Table 2, the tuning of the base properties of the aqueous phase, together with the use of the appropriate leaving group on the alkyne, allowed the obtainment of a range of products **3g**−**q** derived from different cyclic *tert*-butyl ketoesters **1b**−**k** in good yields and generally good enantioselectivities, using the dihydrocinchonine derived salt **5b** as the catalyst (entries 1−11). Two examples demonstrate the possible access to the opposite enantiomer of the products, with nearly similar results, using the quasienantiomeric catalyst **5′b** derived from dihydrocinchonidine (entries 4, 10).

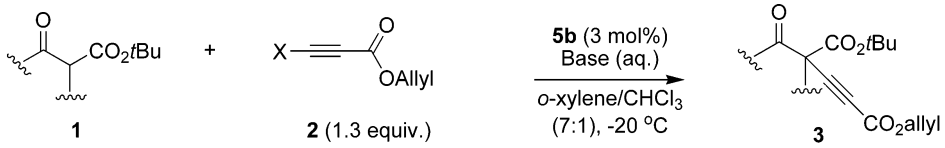
As a first example, we investigated the reactivity of 1-indanone derivative **1b** bearing the ubiquitous 6,7-dimethoxy motif, which afforded the corresponding alkynylated product **3g** in very good yield and enantioselectivity (Table 2, entry 1). A clear evidence of the necessary tuning of the strength of the bulk base in relation to the basicity and reactivity of the β-ketoester employed, came from the catalytic alkynylation reaction using the 6-chloroindan-1-one and the 2-indanone derived β-ketoesters **1c**,**d**. At first, we attempted to perform the reaction under the conditions used successfully for their corresponding 1-indanone derivatives **1a**,**b** (aq K_2CO_3 33%, −20 °C), but obtained a disappointing result in terms of the enantiomeric excess of the adducts **3h** and **3i** (64% and 18% ee, respectively). We attributed these low values to the presence of a background reaction, promoted by the inorganic base. Since a further cooling of the reaction mixture turned out to be unpractical, owing to the freezing of the aqueous phase, we realized that a possible solution relied on the use of an appropriate, milder inorganic base, and after considerable experimentation (see Supporting Information, Tables S1−4) we found that the α-alkynylated products **3h** and **3i** could be obtained with a satisfactory level of enantioselectivity using aq K_2HPO_4 at −20 °C (entries 2, 3). In contrast, the reactions employing the 1-tetralone and 1-benzosuberone derived β-ketoesters **1e** and **1f** proceeded only sluggishly when aq K_2CO_3 was used as the bulk base. However, as observed before (see Table 1) the reaction rate could be dramatically increased by simply employing a more basic aqueous solution (aq Cs_2CO_3), allowing the isolation of the corresponding adducts **3j** and **3k** in satisfactory yields (entries 4, 5), although **3k** was obtained with a rather low enantioselectivity.[28] Similar reaction conditions furnished with very good results compound **3l** derived from the cyclopentanone derived β-ketoester **1g** (entry 6), which proved to be a competent substrate also in the reaction with a β-bromoalkynone such as **2e** (entry 7). The cyclohexanone derivative **1h** was instead found to be rather reluctant in undergoing this alkynylation reaction, as only a combination of a stronger base such as aq K_3PO_4 with the use of the more reactive β-chloroalkyne **2b** as the electrophilic partner could lead to a good isolated yield in the corresponding adduct **3n** (Table 2, entry 8). The excellent enantioinduction (97% ee) observed for this substrate even at +4 °C demonstrates the high efficiency of catalyst **5b** for six-member ring substrates (see also entry 4), confirmed by the results obtained with the cyclohexenone derivatives **1i**−**k**, all giving very high enantioselectivities at the same temperature (entries 9−11). In the last three examples, despite the inherently lower reactivity of the parent β-ketoesters **1i**−**k**, the corresponding products **3n**−**q** could be formed with satisfactory yields simply using a diluted NaOH aqueous solution as the bulk base in the reaction. Although the reaction time in these cases must be controlled to some extent (see Supporting Information), the stability of these adducts in the biphasic reaction conditions with diluted aq NaOH, as well as the absence of decomposition for the cyclopentanone and cyclohexanone derivatives **3l**−**n** in the presence of relatively strongly basic aqueous solutions, is worthy of note, as the hydroxide promoted retro-Dieckmann reaction for this kind of compounds is a known process, reported to occur under mild conditions.[29]

As a final test of the efficiency of the catalytic system we synthesized triisopropylsilyl 2-ether indole **1l**.[30] It was antici-

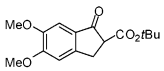
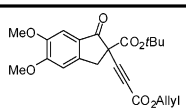
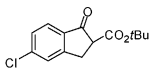
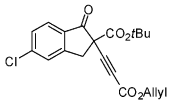
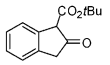
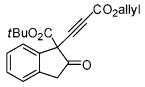
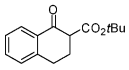
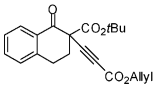
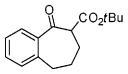
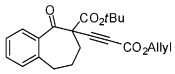
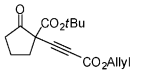
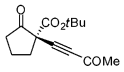
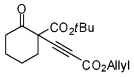
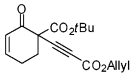
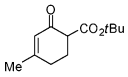
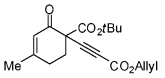
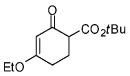
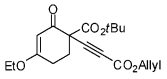
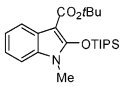
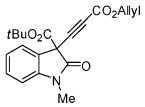
(27) The only described synthesis of **1e** proceeds through a Pd-catalyzed carbonylation reaction from the corresponding bromo derivative: Raju, P. V. K.; Adapa Srinivas, R. *Indian J. Chem., Sect. B* **1992**, *31*, 363. In our hands, the transesterification from the methyl ester in the conditions used for indanones **1a**−**d** (ref 22) proceeded only sluggishly (conversion <50% after several days), though providing the expected product.

(28) Apparently, the present catalytic system does not accommodate relatively flexible substrates: for example, a noncyclic β-ketoester such as *tert*-butyl 2-methyl-3-oxo-3-phenylpropanoate could be alkynylated only with low enantioselectivities (<20% ee).

Table 2. Catalytic Enantioselective Acetylenic Substitution—Scope of the Nucleophile[a]



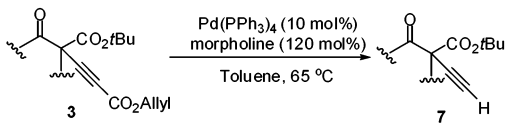
1 2 (1.3 equiv.) 3

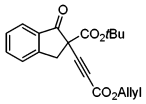
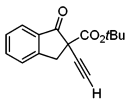
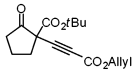
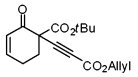
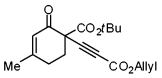
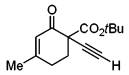
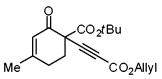
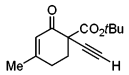
entry	β-ketoester 1		base T (°C)	product 3	yield (%)[b]	ee (%)[c]
1[d]		**1b**	K_2CO_3 33%, -20		**3g** – 89	95
2[e]		**1c**	K_2HPO_4 50%, -20		**3h** – 96	96
3[e]		**1d**	K_2HPO_4 50% -20		**3i** – 72	80
4[d]		**1e**	Cs_2CO_3 66%, -20		**3j** – 82 *ent*-**3j** – 68	98 92[f]
5[e]		**1f**	Cs_2CO_3 66%, -20		**3k** – 85	44
6[d]		**1g**	Cs_2CO_3 66% -20		**3l** – 93	95
7[g]		**1g**	Cs_2CO_3 66% -20		**3m** – 94	(*S*)-84[h]
8[e]		**1h**	K_3PO_4 50% +4		**3n** – 84	96
9[i]		**1i**	NaOH 10% +4		**3o** – 79	97
10[i]		**1j**	NaOH 10% +4		**3p** – 78 *ent*-**3p** – 66	97 87[f]
11[i]		**1k**	NaOH 10% +4		**3q** – 62	93
12[e]		**1l**	KF 33% -20		**3r** – 95	85

[a] Reaction performed with 0.20 mmol of **1** (0.15 M). [b] Isolated yield. [c] The enantiomeric excess was determined by HPLC using a chiral stationary phase. [d] **2a** used as the electrophile. [e] **2b** used as the electrophile. [f] Reaction performed with the quasienantiomeric catalyst **5′b** derived from dihydrocinchonidine. [g] **2e** used as the electrophile. [h] Absolute configuration determined by chemical correlation (see Supporting Information). [i] A total of 2 equiv of **2b** used as the electrophile.

pated that a change of the aqueous base to KF (33%) would facilitate in situ desilylation of the ether indole resulting in release of the oxindole-enolate, which would then undergo the acetylenic substitution guided by the chiral phase-transfer catalyst. To the best of our knowledge, no previous examples of the use of such nucleophiles in phase-transfer catalyzed reactions have been reported. We were therefore very pleased to observe that the reaction occurred smoothly at −20 °C affording the 3-alkynylated quaternary 2-oxindole **3r** in 95% yield and 85% ee. This result is significant because of the

Table 3. Removal of the Alloc-Group by Pd(0)-Catalyzed Deallylation-Decarboxylation



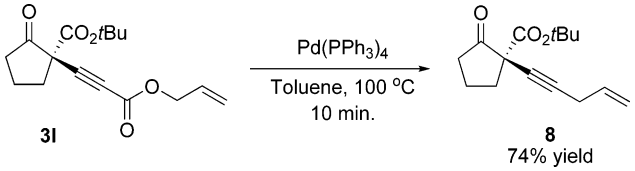
entry	substrate		product		yield (%)[a]
1		**3a**			**7a** – 75
2[b]		**3l**			**7b** – 58
3		**3o**			**7c** – 72
4		**3p**			**7d** – 71
5		*ent*-**3p**			*ent*-**7d** – 69

[a] Isolated yield. [b] $PhSO_2Na$ (1.2 equiv) was used as the allyl-scavenger.

abundance of oxindole containing natural products with an all-carbon quaternary stereocenter in the 3-position of the heterocycle.[31] Fu et al. have previously devised a catalytic asymmetric strategy toward these types of quaternary oxindoles based on the use of chiral nucleophilic catalysts;[32] however, no examples of products bearing an alkynyl substituent were reported.

Product Elaborations. As mentioned above, we anticipated that the allyloxycarbonyl moeity would undergo facile deprotection when subjected to catalytic amounts of Pd(0) and an appropriate allyl-scavenger,[16] and in Table 3 are shown some representative results for this deprotection. In the presence of 10% $Pd(PPh_3)_4$ and 1.2 equiv of morpholine, all compounds tested underwent the deprotection (easily monitored by TLC-analysis) within minutes at 65 °C. After column chromatography, the deprotected compounds **7a**−**d** were obtained in good yields (generally around 70%) and, as expected, with complete fidelity of the enantiomeric excess. In the case of compound **3l** (entry 2) the conditions mentioned above should be avoided. The five-membered ring present in this compound renders the ketone reactive enough to undergo nucleophilic attack by the allyl-scavenger which results in the rupture of the cyclopentanone ring by retro-Dieckmann reaction.[29] It was found, however, that sodium phenyl sulfinate—being less nucleophilic than morpholine—could be used as an alternative allyl-scavenger allowing the isolation of **7b** in 58% yield.

Scheme 5. Synthesis of 1,4-Enynes by Catalytic Decarboxylative $sp-sp^3$ Coupling



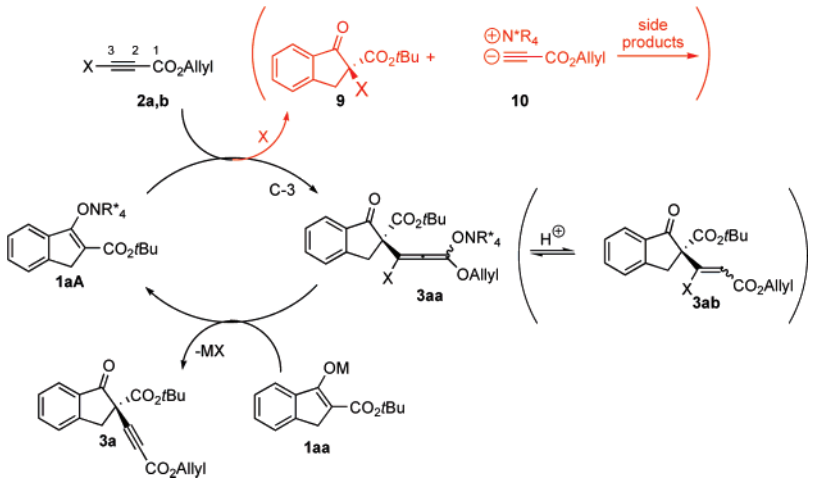
Omitting the allyl scavenger from the reaction mixture allows another important chemical transformation of the α-alkynylated carbonyl compounds. As was recently demonstrated by Tunge et al.[33] the intermediate palladium-allyl-acetylide may undergo reductive elimination resulting in the coupling of the alkyne with the allyl fragment as exemplified for compound **3l** (Scheme 5). The resulting 1,4-enyne **8** was obtained in 74% yield and with unchanged optical purity confirmed by HPLC.

X-ray Crystal Structure and Mechanistic Considerations. Historically, acetylenic substitution was the last type of nucleophilic substitution reaction to be realized in the laboratory[34] and in the years following, the reaction mechanism was heavily debated by various investigators. Although S_N1- and S_N2-type (concerted) substitution mechanisms have been considered, both mechanisms were finally refuted − the former because of the instability of the intermediate alkynyl-cation[35] necessarily involved and the latter because of unfavorable steric and electronic factors. With compounds such as **2** there is now increasing evidence that the mechanism involves carbanionic intermediates, formed by initial addition of the nucleophile to the electrophilic triple bond at C3, and that these intermediates undergo rapid elimination of the nucleofuge reforming the acetylene.[9] Using β-ketoester **1a** as a model, the proposed addition−elimination mechanism is presented in Scheme 6.

Alkali-metal enolate **1aa**, formed from **1a** by deprotonation by the bulk aqueous base, first undergoes cation exchange with the chiral phase-transfer catalyst, which leads to organic soluble ammonium enolate **1aA** as a tight ion-pair. This enolate adds to β-haloalkyne **2** in a highly enantioselective manner, owing to the chiral environment provided by the ammonium salt, forming initially ammonium allenolate **3aa**. The allenolate might undergo elimination of X directly resulting in the release of alkynylated product **3a** or get protonated to form trisubstituted vinylic ester **3ab**.[36] Previous experiments revealed that β-halo substituted enones, which are closely related to **3ab**, do not undergo elimination of HX to any appreciable extent in the presence of aqueous bases such as K_2CO_3 or Cs_2CO_3.[20] As we have never observed the formation of products of type **3ab**, it seems most likely that elimination of the halide occurs from allenoate **3aa** in a comparatively fast process and that the substrate is not released from the phase-transfer catalyst until the elimination has taken place.

(29) (a) Nagao, Y.; Kim, K.; Sano, S.; Kakegawa, H.; Lee, W. S.; Shimizu, H.; Shiro, M.; Katunuma, N. *Tetrahedron Lett.* **1996**, *37*, 861. (b) Sano, S.; Shimizu, H.; Nagao, Y. *Tetrahedron Lett.* **2005**, *46*, 2883.
(30) The parent 3-acyl oxindole was obtained by acylation of *N*-Me-oxindole with *tert*-butyl cyanoformate **6**. These compounds are inherently unstable towards isolation by chromatography on silica gel. To facilitate isolation, the 3-acyl oxindole was converted to the 2-silyl ether indole **1l** (see Supporting Information for details).
(31) For recent total syntheses of compounds possessing this structural feature, see for example: (a) Reisman, S. E.; Ready, J. M.; Hasuoka, A.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 1448. (b) Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 18054. (c) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15395. (d) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505. (e) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36.
(32) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921.
(33) Tunge, J. A.; Rayabarapu, D. K. *J. Am. Chem. Soc.* **2005**, *127*, 13510.
(34) Ott, E.; Dittus, G. *Chem. Ber.* **1943**, *76*, 80.
(35) Angelini, G.; Hanack, M.; Vermehren, J.; Speranza, M. *J. Am. Chem. Soc.* **1988**, *110*, 1298.
(36) For a very nice study on the protonation of allenic enols and enolates, see: Zimmerman, H. E.; Pushechnikov, A. *Eur. J. Org. Chem.* **2006**, 3491.

Scheme 6. Mechanistic Proposal for the Acetylenic Substitution Reaction



As mentioned above, the β-haloalkynes **2** are polyphilic electrophiles, and they might undergo nucleophilic additions also at the halide (Scheme 6) and occasionally on C2.[37] Attack at the halide results in α-halogenation of the nucleophile with concomitant formation of an ammonium acetylide **10**, which can result in a number of side reactions. Protonation of the acetylide releases the free terminal alkynoate to solution and this highly reactive electrophile will undergo nucleophilic additions from residual non-halogenated nucleophile or eventually from another ammonium acetylide. Fortunately, nucleophilic attack at C3 is so strongly favored under the conditions described here that such complications rarely arise. In the few cases mentioned above, an exchange of the halide from bromide to chloride completely eliminated this side reaction. The reason is probably that the more electronegative chlorine atom will be more reluctant in accepting the electron pair from the attacking enolate than the bigger and more polarizable bromine atom.[9]

In the present work and in our previous study on the vinylic substitution reaction we have demonstrated the use of catalysts **5b** and **5′b** in two types of substitution reactions at unsaturated carbon atoms employing 1,3-dicarbonyl compounds of type **1** as the nucleophiles. As these studies, to the best of our knowledge, present the first examples of catalytic enantioselective versions of these fundamental nucleophilic substitutions, we have naturally been very interested in gaining insight into the factors responsible for the high enantioselectivities observed. Repeated attempts finally allowed to us to obtain a single-crystal X-ray structure of catalyst **5b** with *p*-nitrophenolate[38] as the counterion. The structure is shown in Figure 3a,b. When inspecting the structure it should be noted that the asymmetric unit cell contains two molecules of both the catalyst and the counterion as well as several molecules of solvent (water and acetonitrile). The two catalysts in the unit cell were found to have very similar conformations as revealed by superposition studies, and for clarity we have omitted one of them as well as the solvent molecules.

The phenolate counterion was found to reside in a pocket of the catalyst between the quinoline and the quinuclidine rings

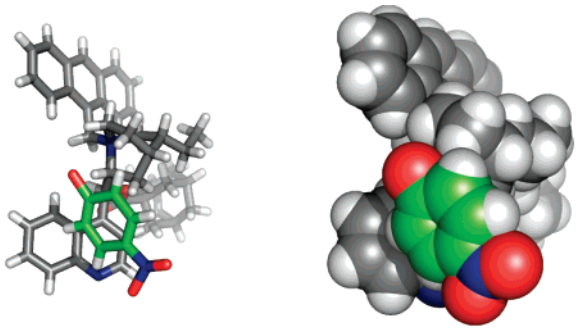


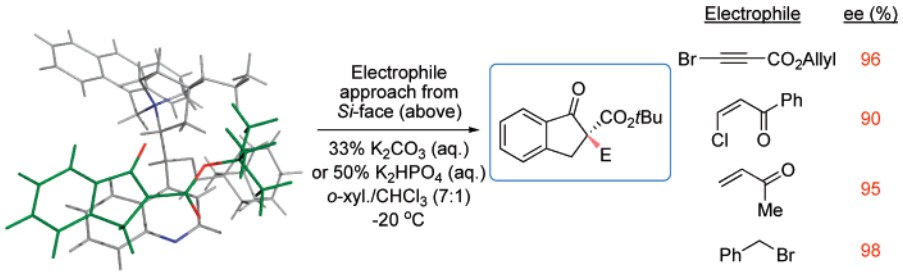
Figure 3. X-ray crystal structure of **5b**−*p*-NO_2PhO$^-$. The carbon atoms of the *p*-nitrophenolate counterion are colored green for clarity.

with a distance of 4.5 Å between the negatively charged phenolic oxygen atom and the quaternized nitrogen atom. Among the X-ray structures previously published of 9-anthracenylmethyl derived cinchona-based phase-transfer catalysts, only two have the C9-hydroxy group protected, and in both cases the protecting group is allyl.[39] These structures were published by Corey et al. in 1997.[40] On the basis of the X-ray data, the authors suggested that negatively charged species might bind the catalyst in the groove between the quinoline and the anthracene ring-systems, which in their case could explain the absolute stereochemistry observed in the alkylation of glycine Schiff bases. In our case, this part of the structure is to some extent blocked by the sterically demanding 1-adamantoyl group.[41] Despite the speculative nature of an attempt to understand the behavior observed in solution through the interpretation of solid-state data, we propose the model shown in Scheme 7 to account for the enantioselectivity and absolute stereochemistry of the alkynylation, in which the *p*-nitrophenolate in the X-ray structure from Figure 3 has been replaced with β-ketoester **1a**.

Positioning the enolate in the space between the quinoline- and quinuclidine rings with the *tert*-butyl ester oriented toward a lipophilic part of the structure effectively blocks the back side (*Re*-face) of the enolate and allows electrophiles to approach from above (*Si*-face). Obviously, the presence of the electrophile must be considered in the transition state of the reaction. However, as is also documented in Scheme 7, the identity of

(37) For the haloalkynes employed in this study, attack at C2 must be considered unlikely because the electron withdrawing group strongly stabilizes the incipient anion resulting from attack at C3. No such stabilization is possible when C2 undergoes nucleophilic attack.
(38) Prepared by ion-exchange with potassium *p*-NO_2-phenolate in MeOH for 2 h followed by aqueous work-up.
(39) By searching of the Cambridge Crystallographic Data Centre.
(40) Corey, E. J.; Feng, Xu.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.
(41) It is worth noting that the overall conformation of our catalyst and the one described by Corey et al. in ref 40 is to a very large extent the same in the solid state (by comparison of the X-ray structures).

Scheme 7. Model of the Enolate-Catalyst Complex and Observed Enantioselectivities with Different Electrophiles



this species seems to matter very little. In fact, besides the two substitution reactions we have documented in this paper and in the previous one,[20] catalyst **5b** also performs the conjugate addition to methyl vinyl ketone as well as the aliphatic nucleophilic substitution using benzyl bromide with excellent enantioselectivities (95% and 98% ee, respectively) and with the same absolute configuration at the stereocenter formed. These results provide further evidence of the efficiency of catalyst **5b** for the asymmetric α-functionalization of β-ketoesters.

Conclusion

In this paper we have presented the first example of a catalytic enantioselective acetylenic substitution reaction. The reaction enables the α-alkynylation of β-ketoesters and 3-acyl oxindoles with excellent enantioselectivities using a readily accessible chiral phase-transfer catalyst under experimentally simple conditions. Furthermore, we have presented that formal addition of an ethynyl unit is possible, as the allyl alkynoates formed in the catalytic reaction are easily deprotected in the presence of Pd(0). Finally, we have, on the basis of X-ray crystallographic data, discussed a plausible catalyst−enolate complex to account for the enantioselectivities and absolute stereochemistry observed in the reaction. We believe that acetylenic substitution, in its catalytic asymmetric variant, might be an important tool for the construction of propargylic stereocenters and that this reaction might be interesting to investigate also in other domains of enantioselective catalysis as well as in asymmetric organic synthesis.

Acknowledgment. This work was made possible by a grant from the Danish National Research Foundation. J.A. thanks Ministerio de Educación y Ciencia of Spain for a postdoctoral fellowship.

Supporting Information Available: Complete experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

JA067289Q