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Ethynylbenziodoxolones (EBX) as Reagents for the Ethynylation of Stabilized Enolates

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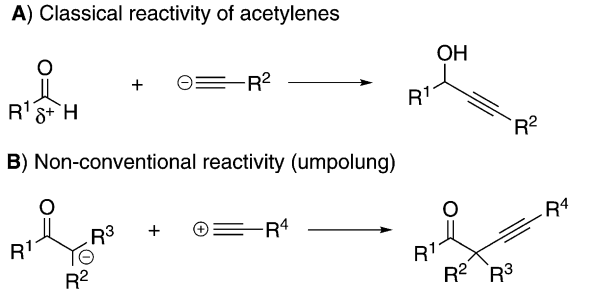
Abstract: Herein, we report a detailed study on the electrophilic alkynylation of cyclic keto esters and amides with ***e***thynyl***b***enziodo***x***olone (EBX) reagents. The structure and stability of this class of reagents is first described more in details. Differential scanning calorimetry (DSC) experiments showed a strong exothermic decomposition with EBX reagents, leading to guidelines for the safe use of these compounds. The extension of the method to aromatic alkynes and a broad range of benziodoxol(on)e reagents is then reported. Based on our preliminary results using *Cinchona*-based phase-transfer catalysts, the enantioselective alkynylation of cyclic keto esters could be achieved. Binaphthyl-derived ammonium catalysts developed by Maruoka and co-workers gave the highest asymmetric induction with up to 79% *ee* for an indanone-derived keto ester. Throughout this work, asymmetric induction was observed only in the case of benziodoxolone reagents, demonstrating their superiority over conventional alkynyliodonium salts. The deeper understanding gained about the factors leading to higher asymmetric induction will be very useful in the future to develop a truly general and highly enantioselective alkynylation method.

Keywords: acetylenes; asymmetric reaction; hypervalent iodine; quaternary centers; *umpolung*

Introduction

In the last decades, acetylene chemistry has been developed considerably. The unique electronic properties and the rigid linear structure of alkynes have led to important applications not only in the field of organic chemistry, but also in biochemistry and material sciences.[1] Furthermore, there are numerous methods for triple bond functionalization, providing a versatile access to more complex molecules and making acetylenes very interesting intermediates in organic synthesis.[2]

As terminal acetylenes are easily deprotonated, the addition of an acetylide anion to an electrophile is one of the most often used reactions for their synthesis. For example, the addition of acetylides to carbonyls gives an efficient access to propargylic alcohols and catalytic asymmetric versions of this reaction have also been developed (Scheme 1, **A**).[3] When considering the large variety of nucleophiles available in organic chemistry, an electrophilic alkynylation method would be highly desirable (Scheme 1, **B**). However, addition of a nucleophile on an alkyne electrophile has been only rarely used. In this case, the *umpolung* of the reactivity of acetylenes is required.[4] A particularly interesting class of nucleophiles is constituted by α-disubstituted carbonyl compounds, as the addition of the triple bond in alpha position allows the formation of all-carbon quaternary centers,



Scheme 1. Classical and non-conventional reactivity of acetylenes with carbonyl compounds.

which cannot be accessed using the normal polarity of acetylenes.

The rare methods reported for the *umpolung* of acetylenes for the alkynylation of enolates are based on the use of halogen acetylenes,[5] lead acetylide reagents[6] and alkynyliodonium salts[7] as electrophilic reagents to introduce the triple bond. However, the scope reported for the α-alkynylation of carbonyl compounds using these methods is limited. Furthermore, there is only one single report of an enantioselective method for the alkynylation of keto esters to generate all-carbon chiral quaternary centers. It was achieved by Jørgensen and co-workers in 2007 using a chiral phase-transfer catalyst.[8] However, alkynylation was possible only using acetylenes bearing an electron-withdrawing group, such as propionic acid derivatives. The synthetically most versatile free acetylenes could not be accessed directly.

Consequently, searching for new electrophilic acetylene synthons for a more general and efficient alkynylation in alpha position to carbonyl functional groups is essential to make the *umpolung* alkynylation approach more synthetically useful. Recently, we have demonstrated the exceptional acetylene-transfer ability of 1-[(trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TMS-EBX, **1a**, Scheme 2) with soft enolates.[9] This method gave direct access to the synthetically most versatile free acetylenes under mild reaction conditions using tetrabutylammonium fluoride (TBAF) both as an activating agent and a base. The use of a cyclic benziodoxolone reagent was essential to improve both efficiency and scope of previously reported methods based on alkynyliodonium salts.[7] Works from our group and others have further demonstrated the utility of EBX reagents in a broad range of electrophilic alkyne transfer reactions.[10]

Alkynylation with TMS-EBX (**1a**) was also successful under phase-transfer conditions using a chiral *Cinchona* ammonium salt as catalyst. Although good conversion was observed under these conditions, only a weak asymmetric induction (40% *ee*) was obtained.[9] Very recently, Veselý and co-workers applied this method for the alkynylation of α-fluorinated sulfone derivatives with up to 61% *ee*.[11] To better understand these results and fully explore the potential of this new class of reagents, we decided to investigate in more detail the reactivity of different new EBX reagents and the influence of substrate structure on reactivity and asymmetric induction.

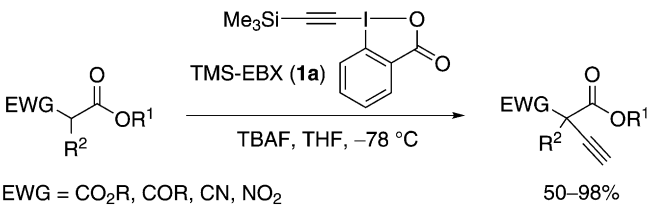
Herein, we report the results of these studies, which demonstrate that the alkynylation is successful for a broad range of benziodoxolone reagents and can be extended to the transfer of aromatic acetylenes. We also give a detailed study of the thermal stability of these reagents, which defines more precisely their safety profile. In the case of cyclic keto esters, a more in-depth study on the influence of the substrate structure and diverse phase-transfer catalysts led to an increase of the asymmetric induction up to 79% *ee* using a binaphthyl-derived ammonium catalyst.

Results and Discussion

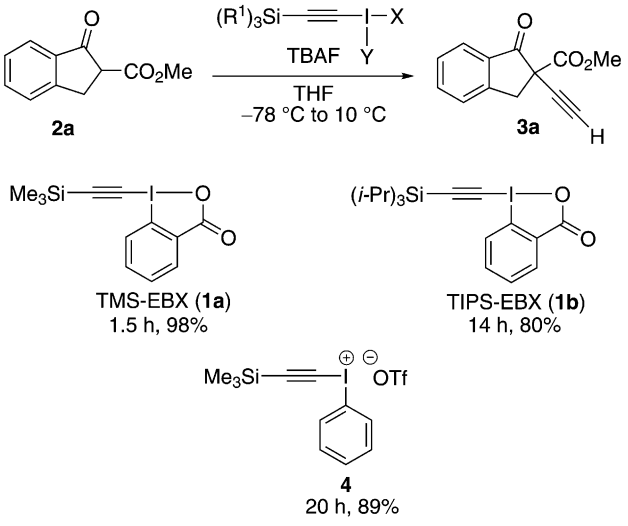
Reagent Structure and Stability

We initiated our study by evaluating the reactivity of different silylated hypervalent iodine reagents under our previously developed conditions using TBAF both as base and fluoride source (Scheme 3).[9] In this case, the reaction of β-keto ester **2a** with hypervalent iodine reagents **1a**, **1b** and **4** gave only free acetylene **3a** in good yield. The reaction with cyclic iodane compounds, especially TMS-EBX (**1a**), is faster than when using iodonium salts. This result is somewhat surprising, as alkynyliodonium salts could reasonably be expected to be more reactive, due to their higher ionic character.

In order to better understand the exceptional reactivity of TMS-EBX (**1a**), we first examined more in detail its solid state structure. TMS-EBX (**1a**) could be recrystallized from a mixture of hexane/CH_2Cl_2



Scheme 2. Alkynylation of activated carbonyl compounds with TMS-EBX (**1a**).



Scheme 3. Alkynylation of keto ester **2a** using EBX reagents **1a** and **1b** and alkynyliodonium salt **4**.

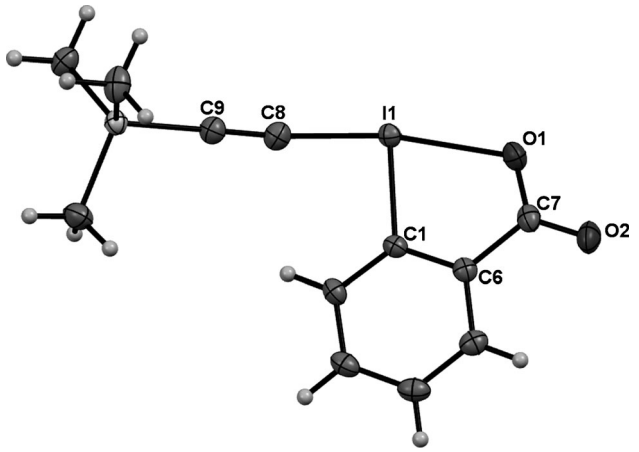


Figure 1. X-ray structure of TMS-EBX (**1a**) showing one molecule. Selected bond lengths: I(1)–C(1): 2.128(2), I(1)–C(8): 2.062 (2), I(1)–O(1): 2.355(1), C(8)–C(9): 1.218(2), C(7)–O(1): 1.290(2), C(7)–O(2): 1.242(2).

(1:1) by slow evaporation of the solvent mixture to give high quality crystals for X-ray analysis (Figure 1).[12] X-ray diffraction confirmed that **1a** had a cyclic structure with a three-coordinated T-shaped hypervalent iodine atom. The distorted trigonal bipyramidal geometry [C(8)–I(1)–O(1) angle: 18°, torsion angle: 3°] left the triple bond free for attack by the nucleophile in the reaction. The bond lengths around the iodine atom are 2.128(2) Å for I(1)–C(1), 2.062(2) Å for I(1)–C(8) and 2.355(1) Å for I(1)–O(1). The length of the I(1)–O(1) bond indicates a strong interaction between I(1) and O(1) and is significantly shorter than the reported bond length for alkynyliodonium salts (2.620 Å).[13] However, it is still longer than a truly covalent I–O bond. Furthermore, the two C(7)–O bonds are of different lengths, but the difference is small [1.290(2) for C(7)–O(1) and 1.242(2) for C(7)–O(2)]. The stronger partial bond character of the I(1)–O(1) bond in comparison to alkynyliodonium salts is probably one of the important sources of the exceptional reactivity of TMS-EBX (**1a**). Non-cyclic alkynyliodonium salts with similar carboxylate substituents are not stable, as they react immediately to form alkynyl esters.[14]

In the solid state, TMS-EBX (**1a**) is further stabilized by strong intermolecular interactions. In particular, the distance between the iodine atom and the carbonyl group of the next molecule is only 2.902 Å, indicating a relatively strong interaction. This results in a pseudo-polymeric structure of TMS-EBX (**1a**) and further explains its high crystallinity. However, this information obtained in the solid state does not allow any definitive conclusions about the behaviour of the reagent in solution.

All hypervalent iodine reagents are high energy compounds. It is consequently important to have enough data on their stability to allow for their safe handling. The thermal stability of TMS- and TIPS-EBX reagents **1a** and **1b** was consequently further investigated by DSC studies.

For TMS-EBX (**1a**), an exothermic behaviour was observed from 117 °C to 181 °C (596 J g^{-1}).[15] Consequently, great care has to be taken when using TMS-EBX (**1a**), as these data very likely indicate the risk of a runaway scenario. The DSC device that we used has a sensitivity of 10 W/kg meaning that as a rule of thumb, with such a sensitivity a safety margin (decrease of onset temperature) of 60 °C is generally considered sufficient for production scales. In our case this would mean to run the reaction below 57 °C to minimize major safety issues (this should be checked by process risk analyses). However, this does not take into account the fact that this degradation may have a lower onset if catalyzed by metals or impurities.

In the case of TIPS-EBX (**1b**) a large exothermic behaviour was observed by DSC from 135 °C to 245 °C (532 J g^{-1}). Consequently, using the same safety margin as before, reactions run with TIPS-EBX (**1b**) below 75 °C could be regarded as safe from the thermal point of view provided no metal-catalyzed or impurity-catalyzed decomposition is occurring. Finally, several qualitative shock sensitivity tests on both TMS- and TIPS-EBX reagents **1a** and **1b** did not lead to any explosion using the compounds synthesized in our laboratory.

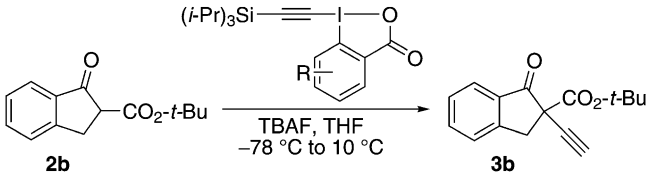
We can conclude from these studies that the manipulation of reagents **1a** and **1b** is relatively "thermally safe" at temperatures below, respectively, 57 °C and 75 °C. However, even in this case great care should be taken when manipulating these reagents, especially on a larger scale, as impurities and metals could potentially act as catalysts and initiate the onset of the decomposition at lower temperatures.

Alkynylation Reactions with Modified Ethynylbenziodoxolones (EBX)

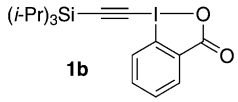
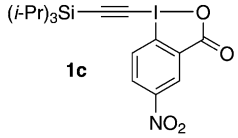
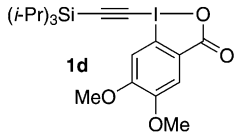
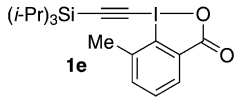
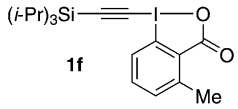
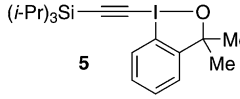
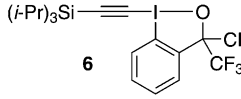
Having examined the structure and stability of the parent EBX reagents, we then decided to examine the influence of chemical modifications both on the benzene core and the benziodoxolone heterocycle in the alkynylation process. Due to their enhanced stability, we decided to focus on triisopropylsilyl-substituted benziodoxolone and benziodoxole reagents for these studies. These reagents had been synthesized previously in our group.[16]

We started our investigation with the alkynylation of *tert*-butyl β-keto ester **2b** under our standard conditions with TBAF as reagent (Table 1). We observed that both reagent **1c** bearing an electron-withdrawing and reagent **1d** bearing an electron-donating group on the benzene ring afforded alkynylated product **3b** in good yields (entries 2 and 3). The reaction was faster

Table 1. Alkynylation of keto ester **2b** using EBX reagents with a modified benziodoxole ring.

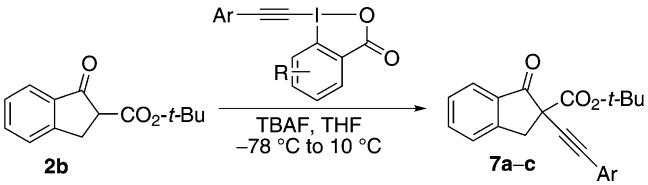


2b **3b**

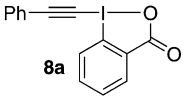
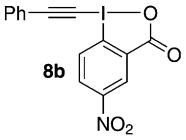
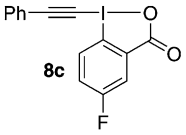
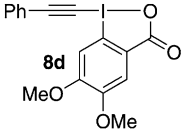
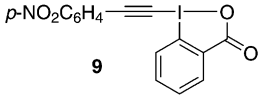
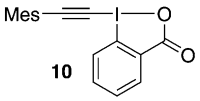
Entry	Reagent	Reaction Time	Yield[a]
1	 **1b**	1.5 h	57%
2	 **1c**	1.5 h	72%
3	 **1d**	48 h[b]	88%
4	 **1e**	5 h	49%
5	 **1f**	1.5 h	47%
6	 **5**	16.5 h[b]	70%
7	 **6**	48 h[b]	49%

[a] *General procedure:* 0.08 mmol keto ester **2b**, 0.105 mmol iodane reagent, 0.105 mmol TBAF, 1.35 mL THF at −78 °C under nitrogen.
[b] Reaction completed at 10 °C.

Table 2. Alkynylation of keto ester **2b** using modified EBX reagents derived from aromatic alkynes.



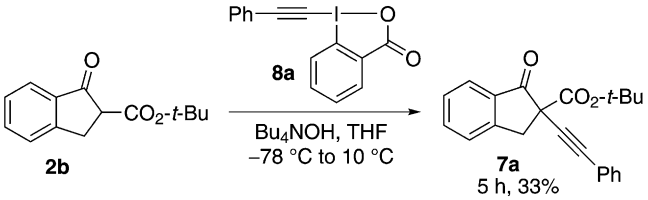
2b **7a–c**

Entry	Reagent	Product (Ar)	Reaction Time (Yield[a])
1	 **8a**	**7a** (Ph)	18 h (48%)
2	 **8b**	**7a** (Ph)	18 h (25%)
3	 **8c**	**7a** (Ph)	18 h (24%)
4	 **8d**	**7a** (Ph)	18 h (57%)
5	 **9**	**7b** (*p*-$NO_2C_6H_4$)	n.r[b]
6	 **10**	**7c** (Mes)	20 h (85%)

[a] *General procedure:* 0.08 mmol keto ester **2b**, 0.105 mmol iodane reagent, 0.105 mmol TBAF, 1.35 mL THF at −78 °C to 10 °C under nitrogen.
[b] No reaction.

with electron-deficient reagent **1c**, however. Methylated TIPS-EBX reagents **1e** and **1f** led to the formation of the ethynylated product **3b** in moderate yields and relatively short reaction times (entries 4 and 5). Finally, we found that TIPS benziodioxole reagents **5** and **6** are also efficient alkynylation reagents under these conditions, although in this case the alkynylation reaction is slower (entries 6 and 7). When considering that a stronger base is liberated upon alkynylation, these results could be interesting in the future to extend the scope of the reaction to less acidic substrates. Furthermore, this result is in sharp contrast to gold-catalyzed reactions involving EBX reagents, as in this case benziodoxole-derived reagents were not efficient alkyne-transfer reagents.[16]

In a second step, we examined if the scope of the alkynylation reaction could be extended to aromatic acetylenes (Table 2). We were delighted to see that the reaction with phenyl-EBX reagent **8a** afforded the corresponding phenylacetylene product **7a** using the TBAF conditions (entry 1). We shortly investigated if modification of the benzene ring would lead to better yields in the alkynylation reaction. The new reagents **8b–d** were consequently synthesized using known procedures.[16,17] Reagents **8b** and **8c** with electron-withdrawing groups on the benzene ring of the benziodoxolone gave low yields (entries 2 and 3). The introduction of electron-donating groups in **8d**, on the other hand, led to a small increase in yield (entry 4). The influence of substituents on the benzene ring attached to the acetylene was even stronger. No reaction was observed for reagent **9** with an electron-with-



Scheme 4. Alkynylation of keto ester **2b** using Bu_4NOH as base.

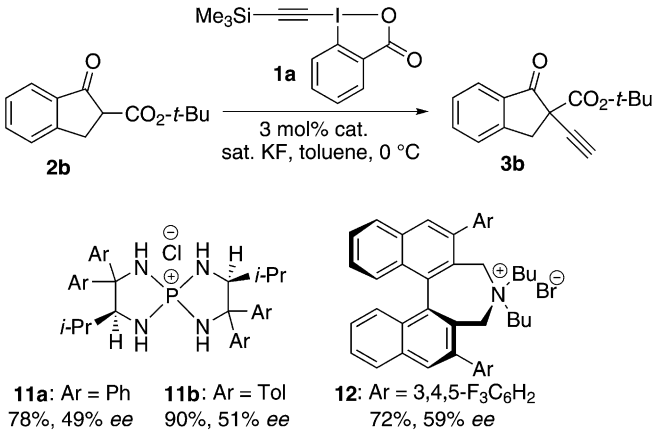
drawing nitro group (entry 5). Unfortunately, the corresponding reagent bearing an electron-donating methoxy group could not be synthesized, as it was not stable. In contrast, we observed that reagent **10** with a mesitylene aromatic group gave the highest yield observed so far (85%, entry 6).

When considering that TBAF had been used because of its higher silicon affinity, there was no real requirement for such a reagent when using aromatic alkynyl reagents. We consequently examined the use of Bu_4NOH to promote the alkynylation reaction using **8a** and keto ester **2b** under similar conditions (Scheme 4). We observed that, even if the reaction afforded the product **7a**, the obtained yield was lower than for the same reaction with TBAF. This could be due to the fact that hydrated TBAF is a milder base, which prevented a competitive decomposition of the reagent.

Asymmetric Akynylation: Catalyst Optimization and Influence of Substrate Structure

In our previous work, we had achieved the alkynylation of substrate **2b** with up to 40% *ee* using a *Cinchona*-based phase-transfer catalyst and TMS-EBX (**1a**). Despite extensive efforts, we were not able to improve on this result using other *Cinchona*-derived catalysts. We consequently decided to examine other classes of potential phase-transfer catalysts. In particular, we became interested by the chiral tetraaminophosphonium salts introduced by Ooi and co-workers in 2008[18] and the binaphthyl-based ammonium salts developed by Maruoka and co-workers.[19] Indeed, the first results obtained using these catalysts were promising (Scheme 5). Phosphonium catalysts **11a** and **11b** led to an increase of the enantioselectivity up to 51%. The most efficient catalyst was commercially available binaphthyl ammonium **12**, for which **3b** was obtained with 59% enantioselectivity.

With this promising lead result obtained with Maruoka's catalyst **12**, we then examined the effect of reaction conditions on the enantioselectivity (Table 3). The influence of solvents was investigated first. A slight decrease in the yield and enantioselectivity was observed in dichloromethane (entry 2). In contrast,



Scheme 5. Asymmetric alkynylation of keto ester **2b**.

the enantioselective excess could be increased from 59% to 65% *ee* using xylene as solvent (entry 3). No further increase was observed when using mesitylene (entry 4).

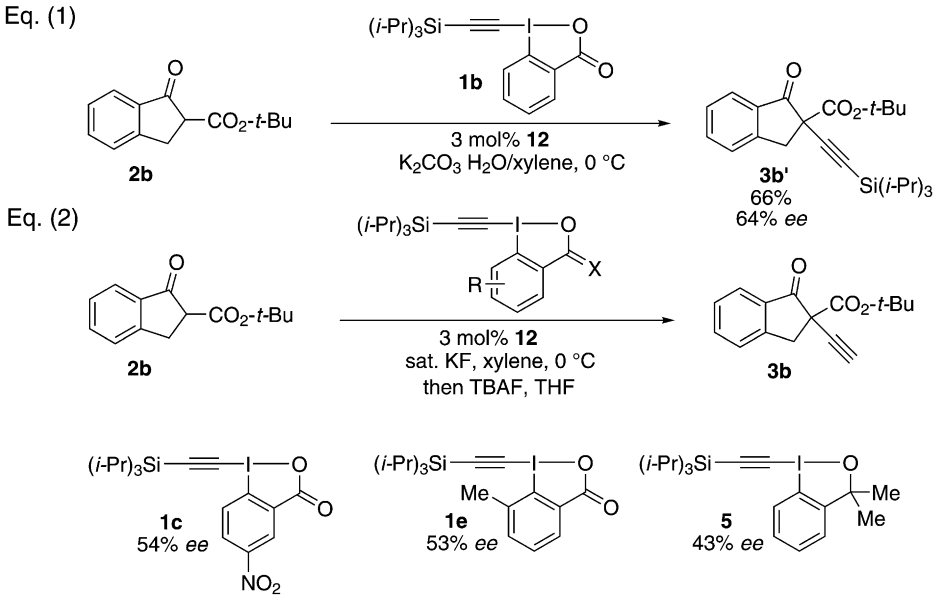
The catalyst loading had no strong influence on the reaction outcome: using 1.5 mol% of catalyst **12** instead of 3 mol%, the yield decreased slightly to 60% and the enantiomeric excess was nearly identical (62% instead of 65%, entry 5).

The influence of the base was investigated next. If a direct background reaction would occur, a reduction of the base concentration could lead to higher enantiomeric excess. However, a lower yield was observed when using a 1 M solution of KF, and no increase in the enantiomeric excess was obtained (entry 6). Changing the base to K_2CO_3 led to a mixture of silylated and free acetylenes with similar *ee* values (entry 7). The use of solid KF as base at low temperature surprisingly led to a high yield of product **3b**,

Table 3. Influence of reaction conditions on the asymmetric alkynylation of **2b** with catalyst **12**.

Entry	Base	Solvent/Temperature	Yield[a]	*ee*
1	$KF_{(sat.)}$	toluene/0 °C	72%	59%
2	$KF_{(sat.)}$	CH_2Cl_2/0 °C	60%	54%
3	$KF_{(sat.)}$	xylene/0 °C	70%	65%
4	$KF_{(sat.)}$	mesitylene/0 °C	64%	64%
5	$KF_{(sat.)}$	xylene/0 °C	60%[b]	62%
6	KF 1 M	xylene/0 °C	30%	61%
7	K_2CO_3 1 M	xylene/0 °C	mixt.[c]	64%[d]
8	$KF_{(sat.)}$	xylene/−78 °C	91%	48%
9	$KF_{(sat.)}$	xylene + MeOH/−50 °C	73%	67%
10	$KF_{(sat.)}$	xylene + *t*-BuOH/−50 °C	82%	64%

[a] *General procedure:* 0.2 mmol **2b**, 1.3 equiv. reagent **1a**, base solution (1 mL), 3 mol% of catalyst **12**, solvent (50 mM in **2b**) under nitrogen.
[b] With 1.5 mol% of **12**.
[c] Mixture of protected and deprotected alkyne product.
[d] The *ee* of deprotected product.



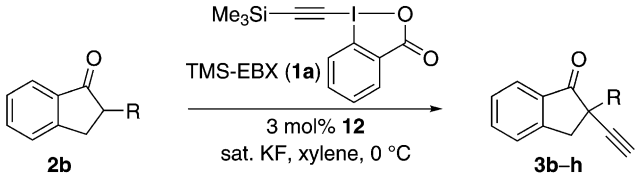
Scheme 6. Influence of reagent structure on enantioselectivity.

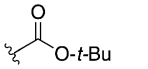
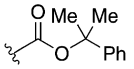
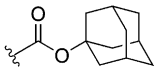
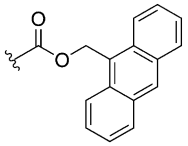
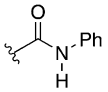
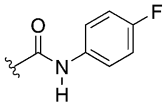
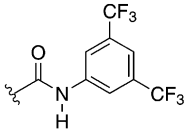
albeit with lower *ee* (entry 8). The *ee* could be restored by using alcohols as additives (entries 9 and 10). Although the results using alcohol additives and solid bases at low temperature still warrant further investigation, we decided to continue our optimization with the more convenient liquid-liquid phase-transfer conditions with saturated KF solutions.

We then shortly investigated if the reagent structure had an influence on the asymmetric induction (Scheme 6). Using TIPS-EBX (**1b**), the silylated product could be obtained exclusively using potassium carbonate as a base, but no change in enantioselectivity was observed [Eq. (1)]. Using potassium fluoride as a base and different benziodoxol(on)e reagents, a mixture of silylated and free acetylenes was usually obtained, which was directly converted to the free acetylenes using TBAF. However, all the investigated reagents led to lower enantioselectivity [Eq. (2)].

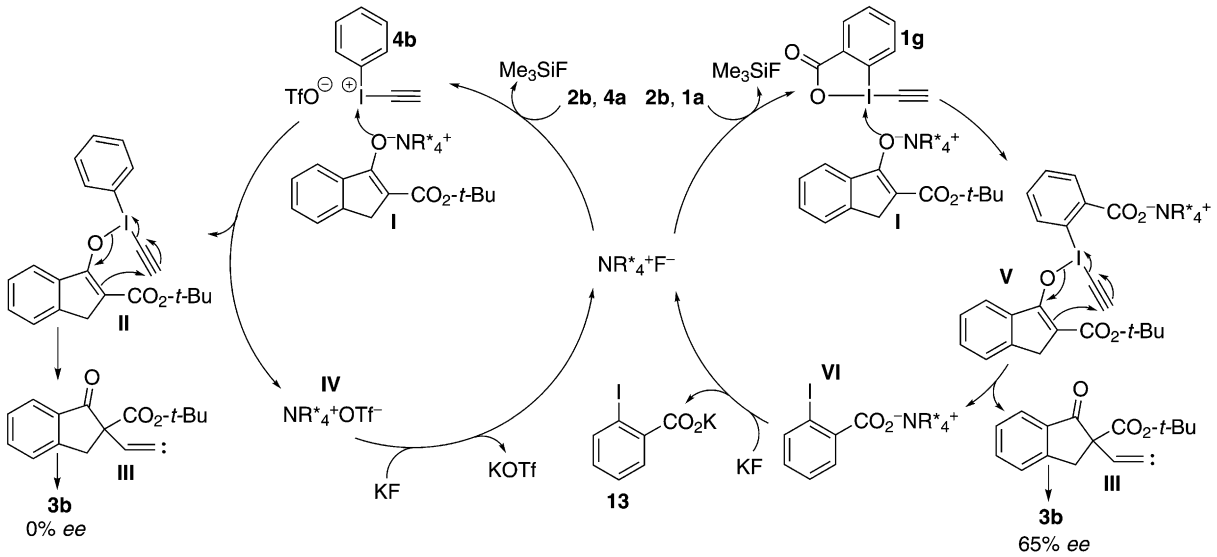
During our studies, we had also observed that the bulky *tert*-butyl ester group on **2b** was required for asymmetric induction. As a next step, we wondered if further fine tuning of this substituent would allow us to reach higher enantioselectivity. We first turned to the introduction of other bulky ester groups on the indanone (Table 4, entries 1–4). We were pleased to see that replacement of one methyl group on the *tert*-butyl by a phenyl group led to an increase of the enantiomeric excess up to 79% (entry 2). Unfortunately, using an even more bulky adamantyl or an anthracenylmethylene group led to lower asymmetric induction (entries 3 and 4). Finally, we investigated if structurally more rigid amides would lead to a better asymmetric induction. Although this class of substrates was alkynylated successfully, a lower enantioselectivity was observed (entries 5–7).

Table 4. Asymmetric alkynylation of cyclic β-keto esters and amides.



Entry	R	Yield[a]	*ee*
1		70%	65%
2		83%	79%
3		99%	55%
4		84%	27%
5		57%	16%
6		93%	30%
7		51%	55%

[a] *General procedure:* 0.20 mmol substrate, 1.3 equiv. TMS-EBX (**1a**), catalyst **12** (0.03 equiv.), saturated KF solution (1 mL), xylene (2 mL), 0 °C to 23 °C.



Scheme 7. Working model for the catalytic cycle with alkynyliodonium salt **4a** and benziodoxolone **1a**.

Throughout our work, asymmetric induction was never observed using alkynyliodonium salts instead of benziodoxolone reagents. At the first glance, this appears highly surprising if the reaction would simply proceed *via* direct C–C bond formation between the catalyst-bound enolate and the hypervalent iodine reagent. However, Olofsson and co-workers have recently made a similar observation in the case of aryliodonium salts: no enantioselectivity could be achieved using different phase-transfer catalysts.[20] To rationalize this result, they proposed that the first step was attack of the oxygen of the enolate on the iodine atom of the hypervalent iodine reagent, which led to decoordination of the catalyst. Logically, no asymmetric induction was possible anymore for C–C bond formation. This result was confirmed by calculation.

Transferred to the case of alkynylation, a similar mechanism would indeed allow rationalization of our observations (Scheme 7). Reaction of alkynyliodonium salt **4a** with fluoride would lead to a fast desilylation and deprotonation of keto ester **2b** to form reagent **4b** and the enolate intermediate **I**. Attack of the oxygen on the iodine will then give neutral intermediate **II** and release the catalyst. Then C–C bond formation would most probably proceed *via* conjugate addition to give carbene **III**, as has been demonstrated by Ochiai and co-workers.[21] Finally, 1,2-hydrogen shift would lead to racemic product **3b**. In the case of neutral TMS-EBX (**1a**), the formation of desilylated reagent **1g** had been indeed observed by NMR.[9] Attack of the oxygen would then lead to intermediate **V**. In contrast to **II**, the chiral catalyst would remain bound to the substrate, and asymmetric induction during the subsequent C–C bond formation would become possible, albeit difficult. Intermediate **V** can then react intramolecularly to give carboxylate salt **VI** and carbene intermediate **III**. In this case, the final 1,2-shift could indeed be supported by a ^{13}C-labelling experiment.[9] This fundamental difference between alkynyliodonium and benziodoxolone reagents makes the latter superior for the design of new enantioselective methods.

Conclusions

In this work, we have studied the electrophilic alkynylation of cyclic keto esters and amides with benziodoxolone reagents in more detail. DSC studies have given a deeper insight into the safety profile of TMS-EBX (**1a**) and TIPS-EBX (**1b**). As both reagents showed a strong exothermic decomposition, adequate care has to be taken when manipulating them. Acetylene transfer could be extended to aromatic alkynes. A broad range of benziodoxol(on)e reagents could be used in the reaction.

Based on our preliminary results using *Cinchona*-based phase-transfer catalysts, the enantioselective alkynylation of cyclic keto esters was further improved. Maruoka's binaphthyl-derived ammonium salt **12** was identified as a better catalyst for asymmetric induction, and up to 79% *ee* could be obtained with an indanone-derived keto ester, which is the highest enantioselectivity reported for this type of reactions. Throughout this work, asymmetric induction could be observed only in the case of benziodoxolone reagents, demonstrating their superiority over conventional alkynyliodonium salts. The deeper understanding gained about the factors leading to higher asymmetric

induction will be very useful in the future to develop a truly general and highly enantioselective alkynylation method.

Experimental Section

General Remarks

See Supporting Information for general experimental details as well as procedures for the preparation and characterization of all precursors and products.

Alkynylation Reactions

General procedure for alkynylation using TBAF: A solution of substrate (1.0 equiv.) and alkynylbenziodoxolone reagent (1.3 equiv.) in dried THF (60 mM) was stirred at −78 °C for 5 min under nitrogen. After this period of time, TBAF (1 M in THF, 1.3 equiv.) was added and the mixture was vigorously stirred at −78 °C. The reaction was monitored by TLC analysis (PET/EtOAc, 4:1, UV and *p*-anisaldehyde) and was complete at −78 °C in the indicated time, or was slowly allowed to warm up to 10 °C during the indicated time. The reaction mixture was quenched with deactivated silica gel and the solvent was evaporated under reduced pressure. The product was purified via flash chromatography (SiO_2, hexane/EtOAc) with the indicated solvent ratio.

General procedure for catalytic phase-transfer alkynylation: A solution of saturated base solution (0.2 M) was added to a solution of phase-transfer catalyst (10 mol%) and alkynylbenziodoxolone reagent (1.3 equiv.) in toluene (50 mM). The mixture was stirred at 0 °C for 5 min under nitrogen. After this period of time, the substrate (1.0 equiv.) was added and the biphasic mixture was vigorously stirred at 0 °C. The reaction was monitored by TLC analysis (PET/EtOAc 4:1, UV and *p*-anisaldehyde). After the indicated time, the reaction mixture was quenched with water and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were recollected, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified *via* silica gel flash chromatography (SiO_2, hexane/EtOAc) with the indicated solvent ratio.

General procedure for catalytic phase-transfer alkynylation using Maruoka's catalyst: A saturated base solution (0.2 M) was added to a solution of phase-transfer catalyst (3 mol%) and alkynylbenziodoxolone reagent (1.3 equiv.) in xylene (50 mM). The mixture was stirred at 0 °C for 5 min under nitrogen. After this period of time, the substrate (1.0 equiv.) was added and the biphasic mixture was vigorously stirred at 0 °C. The reaction was monitored by TLC analysis (PET/EtOAc 4:1, UV and *p*-anisaldehyde) and was complete at 0 °C in the indicated time, or was slowly allowed to warm up to 10 °C during the indicated time. The reaction mixture was quenched with water and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were recollected, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified via silica gel flash chromatography (SiO_2, hexane/EtOAc) with the indicated solvent ratio.

1-[(Trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TMS-EBX, 1a)

Trimethylsilyl triflate (5.54 mL, 30.7 mmol, 1.1 equiv.) was added to a suspension of 2-iodosylbenzoic acid (7.36 g, 28.0 mmol, 1 equiv.) in CH_2Cl_2 (85 mL) at room temperature. The resulting yellow mixture was stirred for 1 h, followed by the dropwise addition of bis(trimethylsilyl)acetylene (6.98 mL, 30.7 mmol, 1.1 equiv.). The resulting suspension was stirred for 6 h at room temperature, during this time a white solid was formed. A saturated solution of $NaHCO_3$ was then added and the mixture was stirred vigorously until completely solubilization of the white solid. The two layers were separated and the combined organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Recrystallization from acetonitrile (5 mL) afforded **1a** as a colourless solid; yield: 7.17 g (20.8 mmol, 74%); mp (dec.): 143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.42$ (dd, $J = 6.4$, 1.9 Hz, 1 H, ArH), 8.19 (m, 1 H, ArH), 7.78 (m, 2 H, ArH), 0.32 [s, 9 H, Si(CH_3)]; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.4$, 134.9, 132.6, 131.7, 131.4, 126.1, 117.2, 115.4, 64.2, −0.5; IR: $\nu = 3389$ (w), 2967 (w), 1617 (s), 1609 (s), 1562 (m), 1440 (w), 1350 (m), 1304 (w), 1254 (w), 1246 (w), 1112 (w), 1008 (w), 852 (s), 746 (m), 698 (m), 639 cm^{-1} (m).

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