DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Copper-Catalyzed Asymmetric Allylic Alkylation of β-Keto Esters with Allylic Alcohols

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

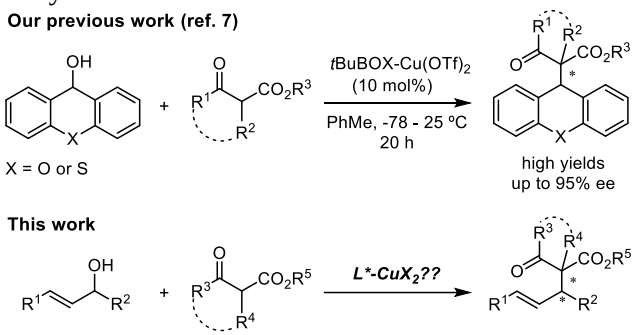
Abstract. The asymmetric allylic alkylation reaction of β-keto esters catalyzed by *t*BuBOX-Cu(OTf)$_2$ employing allylic alcohols as enviromentally friendly electrophilic partner, is herein described. This new protocol renders in general the corresponding allylic products with two consecutive all-carbon stereocenters in good both yields and enantioselectivities and with low to modest diastereoselection. The regioselectivity of the process seems to be governed by the formation of the most stable olefin according to the results obtained when non-symmetrically substituted alcohols were employed. The scope, limitations and mechanistic aspects of the process are also discussed.

Keywords: Asymmetric Allylic Alkylation; Allylic Alcohols; β-Keto esters; Copper; Bisoxazolines

The catalytic asymmetric allylic substitution reaction is a well-established and widespread methodology successfully employed in organic synthesis, which allows the introduction of a vast amount of different nucleophiles in an enantioselective fashion and the creation of new chiral allylic entities containing at least one stereogenic center.[1]

In the last decade, great efforts have been conducted on this important transformation in order to replace the traditionally employed alcohol derivatives (such as carbonates, acetates, phosphates…) as substrates, for the more readily available and environmentally friendly allylic alcohols.[2] However, despite the enormous progresses already accomplished in the area, the asymmetric allylic alkylation reaction, also known as asymmetric Tsuji-Trost reaction, of 1,3-dicarbonyl compounds, employing such substrates is still undeveloped and, to the best of our knowledge, there are only a handful of works reported in the literature on this respect being, most of them, catalyzed by expensive transition-metal based catalytic systems.[3-5] In addition, even scarcer is the use of unsymmetrical 1,3-dicarbonyl compounds, such as β-keto esters, which would render two consecutive all-carbon stereocenters, as nucleophiles.[6]

Continuing with our investigations about the use of π-activated alcohols, able to form stable carbocationic intermediates, in asymmetric alkylation reactions through a S_N1-type process,[7-9] we decided to investigate the copper(II) catalyzed asymmetric alkylation of β-keto esters employing allylic alcohols as alkylating agents (Scheme 1). The results of this study are herein disclosed.[10]

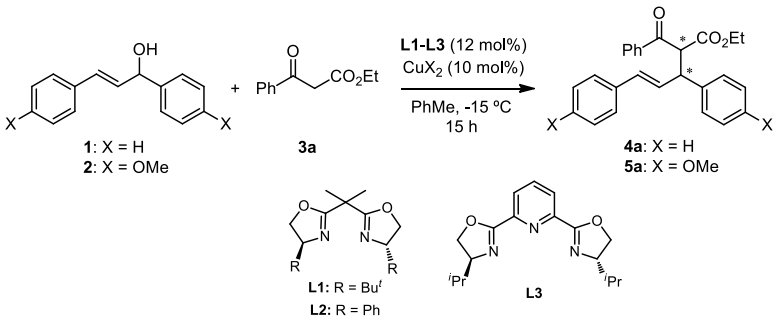


Scheme 1. Alkylation of β-keto esters with activated alcohols.

As starting point, we decided to look for the optimal reaction conditions by checking the reaction between (*E*)-1,3-diphenylprop-2-en-1-ol (**1**), which *a priori* would give rise to a carbocationic intermediate that possesses multiple resonance structures and hence seemingly stable, and keto ester **3a** using Cu(OTf)$_2$ as copper(II) salt. Based on our previous experience with the alkylation of such dicarbonyl compounds with benzylic alcohols,[7] Box-type ligands **L1**-**L3,** toluene and low temperatures (-15 ºC in this case) were the ligands, solvent and the temperature of choice respectively.[11] To our disappointment the reaction produced the desired product but as racemic mixture when using **L1** and **L2** (Table 1, entries 1 and 2). The reason of this behavior might be ascribed to the still high reactivity of the carbocationic intermediate (E = +2.70),[12,13] which apparently favors the racemic background reaction catalyzed by the *in situ* generated TfOH (see Figure 1). [14] With this hypothesis in mind we decided to switch the allylic alcohol to (*E*)-1,3-bis(4-

methoxyphenyl)prop-2-en-1-ol (**2**), which would give rise to a significantly more stable carbocationic specie (E = –1.45).[12] By doing so, we were pleased to observe the formation of product **5a** in high conversion and enantioselectivities, although with poor diastereoselectivity, as expected from a reaction involving a carbocationic intermediate, when *t*BuBOX (**L1**) was the ligand employed (Table 1, entry 3). Changing the ligand to PhBOX (**L2**) and *i*PrPyBOX (**L3**) resulted in worsening results (Table 1, entries 4 and 5). In addition, as somehow expected from our previous work, the reaction using **L1** paired with $Cu(OAc)_2$ did not take place (Table 1, entry 6). Finally, attempts to enhance the diastereomeric ratio by lowering temperature down to –50 ºC were unfruitful since in spite of a slight amelioration achieved, a considerable drop in both conversion and enantioselectivity was obtained (Table 1, entry 7)

Table 1. Optimization of the reaction conditions.[a]

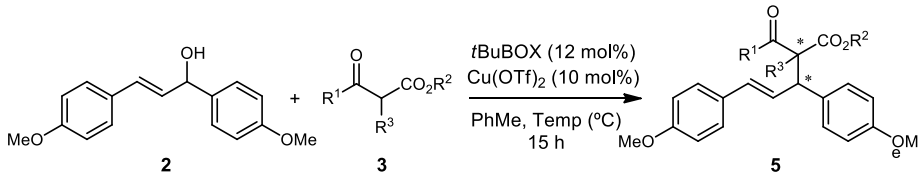


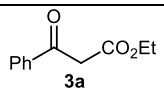
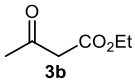
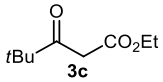
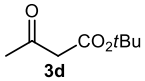
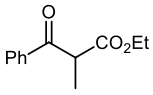
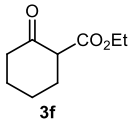
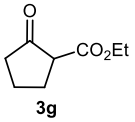
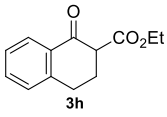
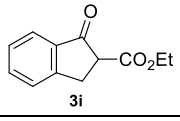
Entry	L	CuX	Product	Conv. [%][b]	*d.r.* [b]	*ee* [%][c]
1	**L1**	$Cu(OTf)_2$	**4**	85	50/50	*rac*.
2	**L2**	$Cu(OTf)_2$	**4**	80	50/50	*rac*.
3	**L1**	$Cu(OTf)_2$	**5**	92	60/40	94/80
4	**L2**	$Cu(OTf)_2$	**5**	85	55/45	33/18
5	**L3**	$Cu(OTf)_2$	**5**	45	50/50	15/<10
6	**L1**	$Cu(OAc)_2$	**5**	<15	—	—
7	**L1**	$Cu(OTf)_2$	5	75[d]	65/35	85/76

[a] Unless otherwise specified, the reaction conditions were: **1** or **2** (0.15 mmol), **2a** (0.225 mmol, 1.5 equiv.), $Cu(OTf)_2$ (10 mol%) and ligand (12 mol%) in 1.5 mL of PhMe at –15 ºC.
[b] Determined by ^{1}H NMR of the crudes.
[c] Determined by HPLC using chiral column Daicel Chiralpak AD-H (see supporting information for details).
[d] Reaction performed at -50 ºC.

Once the optimal reaction conditions were established, different 1,3-keto esters were tested using alcohol **2** as substrates (Table 2). As previously mentioned, **5a** was obtained in good yields, poor diastereoselection and high enantioselectivities in both diastereomers (Table 2, entry 1). Lower yields, even when the reaction was carried out at 0 ºC and using 15 mol% of catalyst loading, were obtained when keto ester **3b** was tested. However, a quite good *d.r*. was obtained (85/15) obtaining, additionally, an excellent 95% *ee* for the major diastereoisomer (Table 2, entry 2). Attempts to further increase diastereo- and enantioselectivities by introducing a bulky group, such as *tert*-butyl, in both the keto (**3c**) and the ester moiety (**3d**) turned out to be unsuccessful, since the reaction failed at low temperatures. The corresponding products, **5c** and **5d**, were only obtained at room temperature with poor or null enantioselection, albeit good diastereoselectivity was observed in the former case (Table 2, entries 3 and 4). Next, acyclic α–methyl substituted keto ester **3e**, which would give rise to the generation of an all carbon quaternary stereogenic center was evaluated,[15] but the reaction failed under optimized conditions. However, at 0ºC good diastereo and enantioselectivities (75/25 and 74%/82% respectively) were achieved although unfortunately with a modest 45% yield (Table 2, entry 5). Rising up the temperature to 25 ºC increased significantly the yield but, as expected, provoked an important detriment in the *d.r*. and the *ee* of product **5e** (Table 2, entry 6). Next, cyclic keto esters were tested. Firstly, six-membered substrate **3f** was assayed, obtaining product **5f** in moderate yield and good enantioselectivities for both diastereoisomer (Table 2, entry 7). To our delight, the reaction afforded the allylation product **5g** in good yield and with an 85:15 diatereomeric ratio, reaching, in addition, high *ee*'s for both diastereomers, 81% and 95%, respectively when **3g** was employed (Table 2, entry 8). In view of the good results obtained with the cyclic keto esters, the more sterically demanding benzocondensed analogs **3h** and **3i** were next tested. However, the reaction became sluggish and only at room temperature the corresponding products were obtained, but as racemic mixtures in both cases (Table 2, entries 9 and 10).

Table 2. Reaction of **2** with different β-keto esters[a]



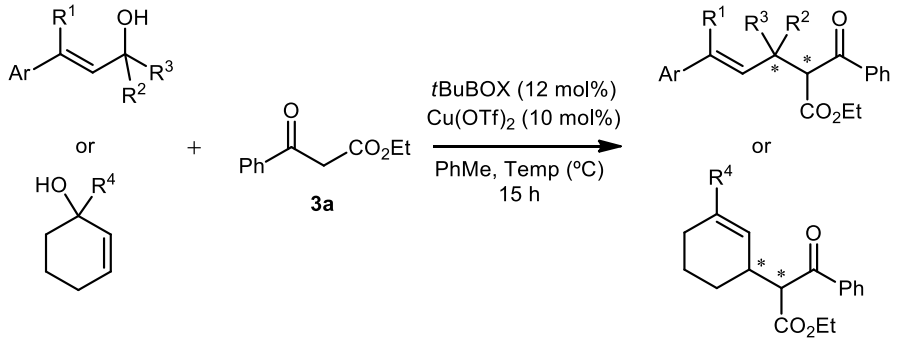
Entry	3	Temp (ºC)	5	Yield [%][b]	*d.r.* [c]	*ee* [%][d]
1	 **3a**	–15	**5a**	79	60/40	94/80
2	 **3b**	0[e]	**5b**	66	85/15	95/13
3	 **3c**	25	**5c**	80	70/30	10/5
4	 **3d**	25	**5d**	85	55/45	*rac.*
5	 **3e**	0	**5e**	45[f]	75/25	74/82
6		25	**5e**	68[f]	55/45	51/28
7	 **3f**	–15	**5f**	67	65/35	70/65
8	 **3g**	–15	**5g**	72	85/15	81/95
9	 **3h**	25	**5h**	79[f]	55/45	*rac.*
10	 **3i**	25	**5i**	81[f]	50/50	*rac.*

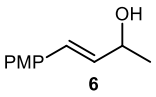
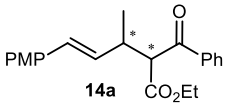
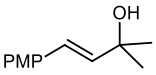
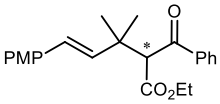
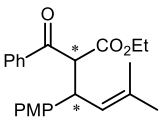
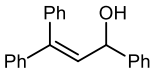
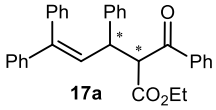
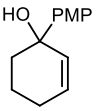
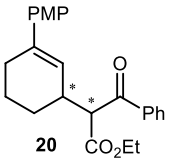
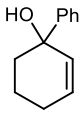
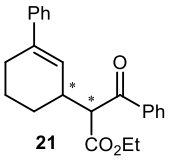
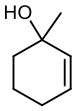
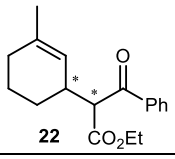
[a] Unless otherwise specified, the reaction conditions were: **2** (0.15 mmol), **3** (0.225 mmol, 1.5 equiv.), $Cu(OTf)_2$ (10 mol%) and *t*BuBOX (12 mol%) in 1.5 mL of PhMe at –15 ºC.
[b] Isolated yields after flash chromatography.
[c] Determined by ^{1}H NMR of the crudes.
[d] Determined by HPLC using chiral columns (see supporting information for details).
[e] Reaction performed with of $Cu(OTf)_2$ (15 mol%) and *t*BuBOX (17 mol%).
[f] Not isolated, estimation of the crude yield from ^{1}H NMR data.

Next, in order to expand the applicability of the process we decided to evaluate other allylic alcohols as alkylating agents in the reaction with keto ester **3a** (Table 3). Firstly, different open chained allylic alcohols possessing an electron donating group were selected. Thus, when alcohol **6** was tested the corresponding product **14a** was only obtained in poor yield, and low diastereo- and enantioselection, even when the reaction was performed at 25 ºC and using 15 mol% of catalyst loading (Table 2, entry 1). With the aim of generating a more stable carbocationic intermediate, the allylic alcohol **7** containing an extra methyl group was synthesized. The reaction of such alcohol with keto ester **3a** gave rise to the formation of regioisomers, being the product **16a**, which arise from a double bond isomerisation, the major one. Unfortunately, this last product was obtained in a 52:48 diastereomeric ratio and with low enantioselectivities. By the contrary, a modest 46% *ee* was observed for the minor regiosiomer **15a** (Table 2, entry 2). Attempts to favour the formation of this last regioisomer by lowering the temperature (0 ºC) were unfruitful and under these conditions the yield dropped considerably. On the other hand, as

somehow expected, the enantioselectivity was increased up to 68% (Table 2, entry 3). Disappointingly, the use of alcohol **8**, which after dehydration would give rise to the formation of a rather stable, although sterically crowded, carbocationic intermediate (E = +0.98),[12] gave rise to the corresponding product **17a** as racemic mixtures and only when 15 mol% of catalyst loading and 25 ºC were employed (Table 2, entry 4).

Table 3. Alkylation of **3a** with different alcohol[a]



Entry	Alcohol	Temp (ºC)	Product(s)	Yield [%][b]	*d.r.* [c]	*ee* [%][d]
1	 **6**	25[e]	 **14a**	37[f]	55/45	18/30
2	 **7**	25	 **15a** (12%)	83	52/48	46 (**15a**) 8/8 (**16a**)
3		0	 **16a** (88%)	42[f]	52/48	68 (**15a**) 20/10 (**16a**)
4	 **8**	25[e]	 **17a**	85	50/50	*rac.*
5	 **10**	–15	 **20**	73	70/30	96/82
6	 **11**	25	 **21**	40[f]	80/20	82/36
7	 **12**	25	 **22**	<15	n.d.	n.d.

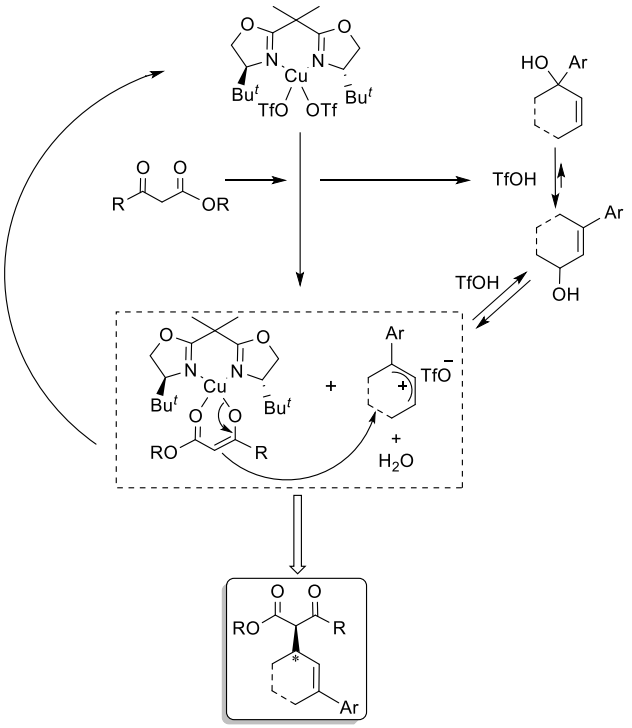
[a] Unless otherwise specified, the reaction conditions were: alcohol (0.15 mmol), **3a** (0.225 mmol, 1.5 equiv.), $Cu(OTf)_2$ (10 mol%) and *t*BuBOX (12 mol%) in 1.5 mL of PhMe.
[b] Isolated yields after flash chromatography.
[c] Determined by ^{1}H NMR and/or GC of the crudes.
[d] Determined by HPLC using chiral columns (see supporting information for details).
[e] Reaction performed with of $Cu(OTf)_2$ (15 mol%) and *t*BuBOX (17 mol%).
[f] Not isolated, estimation of the crude yield from ^{1}H NMR data.

Next, since the results with acyclic allylic alcohols were unsuccessful, we decided to evaluate the behaviour of allylic cyclic alcohols. We were pleased to observe that, under optimized conditions, alcohol **10** produced the allylation product **20** as a sole regioisomer in high yield and diastereo- and enantioselectivity (Table 3, entry 6). Encouraged by this result, alcohol **11** was then tested and, despite the fact of obtaining high diastereo- and enantioselectivity for compound **21**, low yields were obtained even when the reaction was performed at room temperature (Table 3, entry 7). As somehow

expected the replacement of the phenyl group by a methyl one caused the reaction failure (Table 3, entry 8).

Concerning the regiochemical course of the process, the results observed in the reaction of **3a** with alcohols **7**, **10** and **11** (Table 3, entry 2, 3, 6 and 7) clearly point towards a rearrangement of the allylic alcohol. This isomerization, which has been previously observed by us[9c,d] and other groups when using such substrates in the presence of a Lewis or Brønsted acid,[16] could take place before the reaction with the *β*-keto ester. Thus, the formation of the most energetically favorable olefin seems to govern the regiochemistry of the reaction rather than the stability of the carbocationic intermediate.

Once the regiochemical outcome was established and assuming that an S_N1-type reaction occurred, a tentative mechanism was proposed as follows (Scheme 2). Firstly, the catalytic system *t*BuBOX-$Cu(OTf)_2$ would coordinate the keto ester through the enolate, hence liberating a substechiometric amount of TfOH which would be enough not only to form the corresponding carbocation but also to promote the alcohol isomerization towards the formation of the most stable olefin.[16] Finally the S_N1-type reaction would take place in a enantiospecific way onto the planar carbocationic intermediate which would explain the low *d.r.* observed in most of the cases.[17] Regarding, the stereochemistry of the new formed all-carbon stereogenic centers, and despite several trials performed, we were not able to determine the absolute configuration of these new synthesized products. Nevertheless, (*R*)- configuration at the center placed in the keto ester moiety could be assumed. This hypothesis arise from the fact that the catalytic complex and the *β*-keto esters employed in this work are exactly the same to those employed in our previous work, in which the (*R*)-configured alkylated *β*-keto ester products seemed to be obtained when xanthydrols were the alkylating agents.[7]



Scheme 2. Proposed reaction mechanism

In summary, in this work we have disclosed the application of the complex $Cu(OTf)_2$-*t*BuBOX as catalyst for the asymmetric allylic alkylation of *β*-keto esters employing allylic alcohols as alkylating agents. Although the scope of the methodology herein presented seems to be somehow narrow, this simple and environmentally benign process avoids the use of expensive transition metal complex and generates only water as by-product. By using this new protocol different keto esters were successfully alkylated, generating two consecutive all carbon stereogenic centers. The best results, in terms of both yield and enantioselectivity, were achieved in those cases where a stable carbocationic intermediate was formed. The reaction mechanism seems to proceed through an S_N1-type reaction, which could explain the low diastereoselection observed in the majority of cases. In addition, the results observed suggest an TfOH catalyzed *in situ* isomerization of the alcohol towards the most energetically stable olefin prior the reaction to occur, thus governing the regioselectivity of the process.

Experimental Section

General procedure for the asymmetric allylic alkylation of *β*-keto esters with allylic alcohols.

Onto an evacuated, oven-dried and septum-capped flask containing *Bu*^{t}-BOX ligand (**L1**, 5.4 mg, 0.018mmol, 12 mol%) and $Cu(OTf)_2$ (5.4 mg, 0.015 mmol, 10 mol%) under argon atmosphere, toluene (0.5 mL) was added. The complex was stirred at 25 ºC for 90 min. After this time, the flask was placed in a cooling bath at the corresponding temperature and stirred for 10 min. Then, *β*-keto ester (0.21 mmol, 1.5 equiv.) was added and stirred for an

additional 10 min. Next, a solution of the corresponding alcohol (0.15 mmol) in toluene (1 mL) was finally added and the reaction mixture stirred for 15 h. After this time, saturated NH_4Cl (3 mL) was added and the mixture extracted with ethyl acetate (3 x 5 mL). The organic phases were dried ($MgSO_4$) and evaporated. The crudes were purified by flash chromatography. ***NOTE:*** Slight to moderate racemization was observed in some cases after flash chromatography was carried out. In addition, the chiral adducts *MUST* be kept in the freezer (-20 ºC) to avoid racemization.

Acknowledgements

University of Alicante (VIGROB-173, GRE12-03), and Spanish Ministerio de Economía y Competitividad (CTQ2015-66624-P) are gratefully acknowledged for financial support (Project).

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