Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201800914

Link to VoR: http://dx.doi.org/10.1002/adsc.201800914

10.1002/adsc.201800914

UPDATE

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

Regio- and Stereoselective Chan-Lam-Evans Enol Esterification of Carboxylic Acids with Alkenylboroxines.

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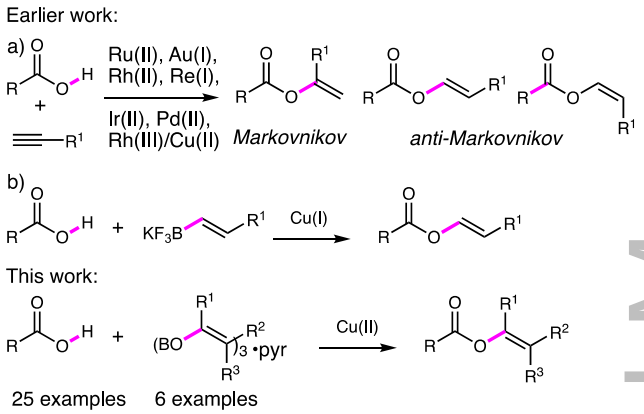
Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. Efficient and scalable Cu(II)-mediated enol esterification methodology of carboxylic acids from alkenyl boroxines and boronic acids is presented. The reaction shows a wide scope in aliphatic and aromatic carboxylic acids in combination with several alkenyl boroxines. In the case of 2-substituted alkenyl boroxines the double bond configuration was fully retained in the enol ester product. Also N-hydroxyimides and imides could be transformed in the respective amidooxy vinyl enol ethers and vinyl enamides. Finally, with the exception of methionine, all other 19 canonical amino acids showed their compatibility to give the enol esters in a stereoselective fashion.

Keywords: Cu(II) catalysis; Enol esters; Chan Lam Evans reaction; Activated esters; Boroxines

Enol esters are valuable starting materials in polymer chemistry[1] but may also serve as activated esters[2] and as substrates for several useful transformations.[3] Currently, highly efficient methods exist for the preparation of enol esters of which the transition-metal catalyzed addition of alkynes to carboxylic acids stands out.[4] Although several transition metals have been reported for this transformation, ruthenium-catalyzed enol esterifications are most widely described.[5] By starting from a terminal alkyne three products may be formed. Two regioisomers emerge from Markovnikov or anti-Markovnikov addition of which the latter also may give both double bond configurations (Scheme 1a). Although significant progress has been made, full control of regio- and stereochemistry can still be problematic.[6] This hampers further functionalization of enol esters in which the stereochemical outcome depends on the double bond geometry (*i.e.* hydroformylation,[3a] hydrogenation[3b]). Furthermore, in all transition metal catalyzed enol esterifications, precious metals were used. Herein, we report the use of the cheap and abundant first-row transition metal Cu(II) as the catalyst for the Chan-Lam-Evans (CLE)-type enol esterification of carboxylic acids from alkenyl boroxine pyridine complex or boronic acids with full retention of the regio- and stereochemistry in both the enol ester and substrate.



Scheme 1. Outline of this work.

Recently, the Batey group has shown the utility of the CLE reaction in the preparation of enol esters starting from potassium alkenyltrifluoroborate salts (Scheme 1b).[7] In earlier work we and others have shown that carboxylic acids can be conveniently transformed into aryl esters using the CLE reaction from aryl boronic acids or boroxines.[8] Starting from arylboroxines, the CLE reaction even allows C-terminal activation of peptides as aryl esters that were used in subsequent amidation reactions without loss of stereointegrity.[8b] In this letter we report the efficient synthesis of a wide variety of enol esters from commercially available alkenylboronic acids and boroxine pyridine complexes and some useful follow up transformations such as aminolysis, trans(thio)esterification, reduction, aminal and cyanohydrin ester formation. By using the same conditions as developed for the arylesterification from aryl boroxines, *i.e.* $Cu(OTf)_2$/1,3-diethylurea as the catalyst, Et_3N as the base in THF at 50 °C under a balloon of air, starting from benzoic acid and commercially available vinyl boroxine pyridine complex, vinyl benzoate **1a** was obtained in high yield (Scheme 2). Although using 0.4 equiv of $Cu(OTf)_2$

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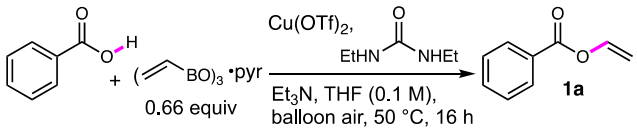
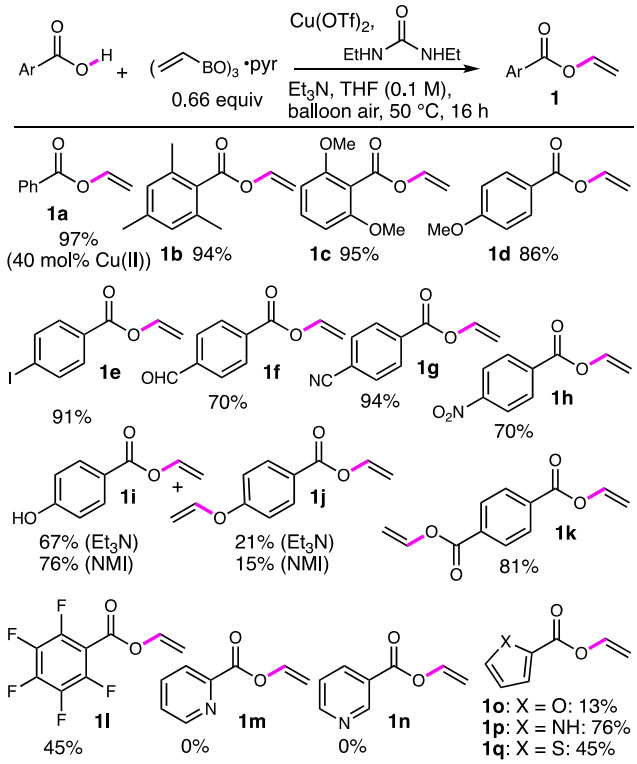
was considered as optimal, far lower catalyst loadings may be used whereby longer reaction times and a somewhat lower yield must be accepted.



$Cu(OTf)_2$ (mol%)	Time (days)	Yield
40	1	88%
40	3	97%
20	1	58%
20	3	89%
10	1	5%
10	3	81%

Scheme 2. Optimization of the CLE-mediated enol esterification from vinyl boroxine.

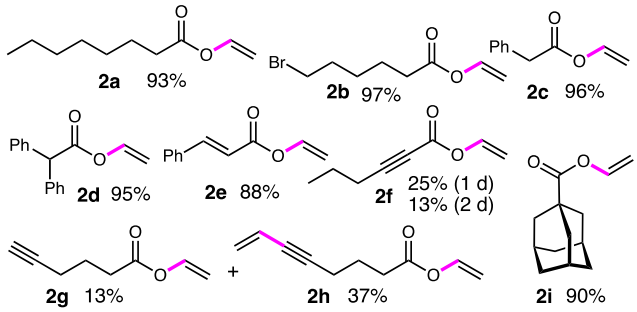
After some optimization, vinyl benzoate **1a** was obtained in near quantitative yield prompting us to study the scope with respect to the type of aryl carboxylic acid (Scheme 3).



Scheme 3. Scope aromatic and heteroaromatic carboxylic acid enol esterification.

The reaction proved to be insensitive to steric hindrance as vinyl 2,4,6-trimethylbenzoate **1b** was obtained in 94% isolated yield. Both electron poor (4-NO_2, 4-CN, 4-CHO, 4-I) and electron rich (4-OMe, 2,6-diOMe) benzoic acids gave vinyl esters **1d-h** in good yields ranging from 70 to 95%.By starting from 4-hydroxybenzoic acid the acidic phenolic hydroxylgroup also participated in the reaction resulting in concommittant vinyl ether formation giving both **1i** and **1j**. By replacing Et_3N by the milder base N-methylimidazole, formation of the vinyl ether could be suppressed somewhat to give the vinyl ester **1i** in 76% yield along with 15% of the bisvinylated product **1j**.Vinyl pentafluorobenzoate **1i** was obtained in a significantly lower yield of 45%. Terephthalic acid could be bis-vinylated to give **1k** in 81% yield. Among the heteroaromatic carboxylic acids both 2-picolinic and nicotinic acid showed no conversion to **1m**, **n** at all. These N-centered heterocycles formed insoluble Cu-complexes hampering CLE-coupling. Vinyl furan-2-carboxylate **1o** was obtained in 13% yield only. On the other hand, vinyl esterification of pyrrole-2-carboxylic acid and thiophene-2-carboxylic acid gave **1p** and **1q** in 76% and 45% isolated yield.

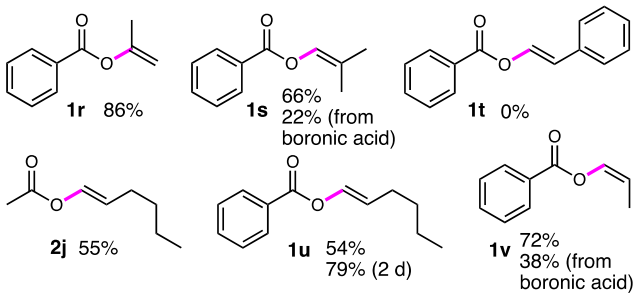
As shown in Scheme 4, also aliphatic and α,β-unsaturated carboxylic acids are suitable substrates.



Scheme 4. Scope non-aromatic carboxylic acid enol esterification.

The vinyl esters **2a-d** of *N*-octanoic, 6-bromohexanoic, phenylacetic and diphenylacetic acid were isolated in yields ranging from 93% to 97%. Also cinnamic acid gave clean conversion to the vinyl ester **2e** in 88% isolated yield. Hex-2-ynoic and hex-5-ynoic were troublesome substrates giving the vinyl esters **2f** and **2g** in yields of 25% and 13% only. Remarkably, the terminal alkyne of vinyl hex-5-ynoate was additionally vinylated to give **2h** in 37% yield. Because of the high affinity of Cu-ions for alkynes these low yields and side reactions were not unexpected. The insensitivity towards sterics was shown by obtaining vinyl ester **2i** of 1-adamantanecarboxylic acid in 90% yield.

Next, substituted vinylboroxines were used as substrates (Scheme 5).



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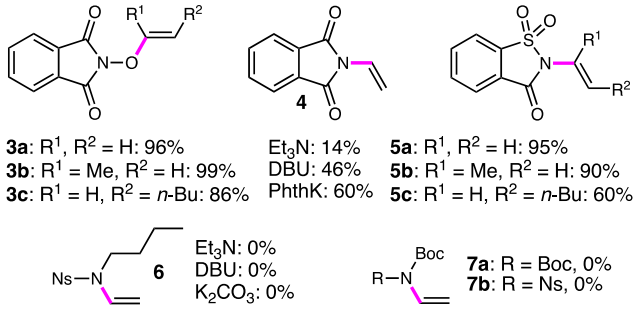
Scheme 5. Scope alkenyl boroxines or boronic acids on carboxylic acid enol esterification.

Using the same conditions, prop-1-en-2-yl benzoate **1r** was obtained from benzoic acid in 86% yield. (2-Methylprop-1-en-1-yl)boroxine gave the corresponding enol ester **1s** in 66% isolated yield. For unknown reasons, this boroxine failed to give the pyridine complex. Starting from the boronic acid, the yield providing **1s** dropped to 22%. Surprisingly, (*E*)-styryl benzoate **1t** could not be obtained at all. Enol esterification of acetic acid and benzoic acid from (*E*)-hex-1-en-1-ylboroxine gave **2j** and **1u** in moderate yields albeit with complete retention of the double bond configuration. After stirring for 2 d the yield of (*E*)-hex-1-en-1-yl benzoate (**1u**) was raised to 79%. Similarly, (*Z*)-prop-1-en-1-ylboroxine selectively gave the *Z*-configured enol ester **1u** in 72% isolated yield. The low yield of 38% for **1v** found after starting from the boronic acid once again underscores the superior reactivity of the boroxines.

Due to the facile enol etherification for phenolic hydroxyl groups as observed as a side reaction (*vide supra*), also other acidic O-, and N-centered nucleophiles were evaluated as substrates (Scheme 6).[10]



Scheme 6. Miscellaneous amidooxy enol ether and enamide formations.

Indeed, at N-hydroxy phthalimide a vinyl, 2-propenyl or 1-hexenyl group could be installed to give **3a-c** in yields of 96%, 99% and 86%, respectively. Phthalimide (pK_a = 9.9) is 3.6 pKa units less acidic than N-hydroxyphthalimide (pK_a = 6.3) and consequently transformation into vinyl amide **4** using the same conditions was accomplished in 14% yield only. By introducing DBU as a stronger base or by starting from potassium phthalimide the yield was improved to 46% and 60%, respectively. Saccharine showed to be an excellent substrate giving the N-vinyl product **5a** in 95% isolated yield. Also the 2-propenyl or 1-hexenyl esters **5b**, **c** were made in 90% and 60% yield. The less nucleophilic acyclic N-centered nucleophiles could not be coupled. N-vinylation of N-butyl-2-nitrobenzenesulfonamide and even the very acidic *tert*-butyl ((2-nitrophenyl)sulfonyl)carbamate and di-*tert*-butyl iminodicarboxylate gave no reaction towards **6** or **7a**, **b** at all using several bases. Enol esters have been used in direct amidation reactions and as such would circumvent expensive coupling reagents.[2b, 8b] Amino acid[2a, 9a,b] and peptide enol esters[9c] have also shown their utility as acyl donors in biocatalytic esterification and amidation reactions. Therefore, a set of representative N-protected α-amino acids were reacted with vinyl boroxine under the CLE-conditions (Table 1). The two enantiomers Ac-Phe-OCH=CH_2 (**8a**) and Ac-D-Phe-OCH=CH_2 (**8b**) were obtained in isolated yields of 94% and 93%, respectively and chiral HPLC analysis showed that in both cases no detectable racemization had occurred. Also, the common Fmoc, Boc and Cbz carbamate protective groups and amino acids lacking nucleophilic sidechains such as Trp and Val and even Asn showed their compatibility with CLE-type enolesterification to give **8c-h** all in high yields.

Table 1. Amino acid enol esterification.

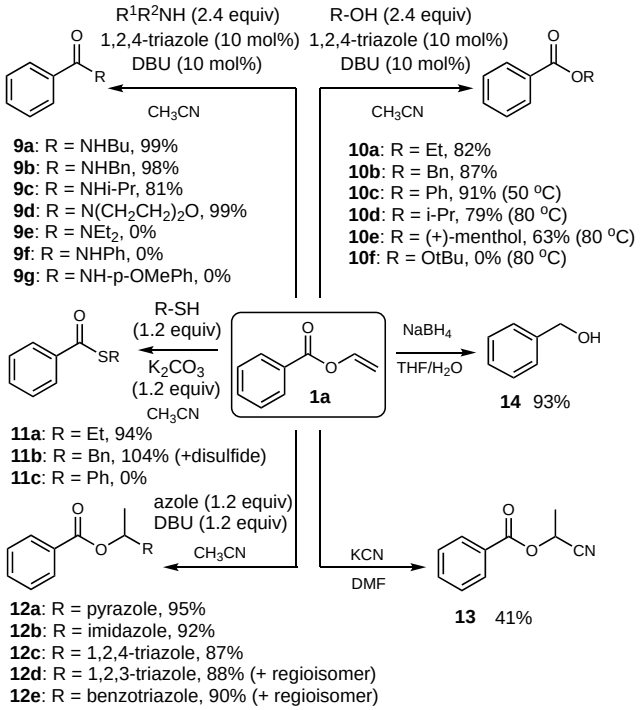
starting amino acid	product	yield (ee)
Ac-Phe-OH	**8a**: Ac-Phe-OCH=CH_2	94% (99.1%)
Ac-D-Phe-OH	**8b**: Ac-D-Phe-OCH=CH_2	93% (99.8%)
Fmoc-Phe-OH	**8c**: Fmoc-Phe-OCH=CH_2	94%
Boc-Phe-OH	**8d**: Boc-Phe-OCH=CH_2	93%
Cbz-Phe-OH	**8e**: Cbz-Phe-OCH=CH_2	94%
Fmoc-Trp-OH	**8f**: Fmoc-Trp-OCH=CH_2	89%
Fmoc-Val-OH	**8g**: Fmoc-Val-OCH=CH_2	99%
Fmoc-Asn-OH	**8h**: Fmoc-Asn-OCH=CH_2	84%
Fmoc-Tyr-OH	**8i**: Fmoc-Tyr-OCH=CH_2	75%
	8j: Fmoc-Tyr(-OCH=CH_2)-OCH=CH_2	20%
Fmoc-Tyr(OtBu)-OH	**8k**: Fmoc-Tyr(OtBu)-OCH=CH_2	99%
Boc-Ser-OH	**8l**: Boc-Ser-OCH=CH_2	54%
Fmoc-Ser(OtBu)-OH	**8m**: Fmoc-Ser(OtBu)-OCH=CH_2	99%
Fmoc-Arg(Pmc)-OH	**8n**: Fmoc-Arg(Pmc)-OCH=CH_2	88%
Fmoc-Lys(Boc)-OH	**8o**: Fmoc-Lys(Boc)-OCH=CH_2	97%
Fmoc-His(Trt)-OH	**8p**: Fmoc-His(Trt)-OCH=CH_2	<62%[a]
Boc-His(Boc)OH	**8q**: Boc-His(Boc)-OCH=CH_2	36%
Fmoc-Met-OH	**8r**: Fmoc-Hse lactone	64%
Fmoc-Cys(Acm)-OH	**8s**: Fmoc-Cys(SCH=CH_2)-OCH=CH_2	29%
Ac-Cys(Boc)-OH	**8t**: Ac-Cys(Boc)-OCH=CH_2	87%

[a] The exact yield could not be determined due to the presence of copper residues

For both tyrosine and serine hydroxyl group protection was required to obtain high yields (**8i**, **j** vs. **8k** and **8l** vs. **8m**). Suitably protected arginine and lysine gave the corresponding enol esters **8n** and **8o** in high yields. Histidine sidechain trityl protection gave enol ester **8p** although in irreproducible yields and contamination by copper residues. Fortunately, Boc-His(Boc)-OCH=CH_2 (**8q**) could be obtained in pure form albeit in a moderate yield of 36% yield. Methionine showed to be incompatible giving the corresponding homoserine (Hse) lactone **8r** in 64% isolated yield, most probably due to copper-mediated cationic activation of the thioether inducing nucleophilic attack of the carboxylate group. Also the nucleophilicity of the cysteine sulfur had to be blocked completely. Acm sulfhydryl protection gave Boc-Cys(SCH=CH_2)-OCH=CH_2 (**8s**) as a side product in 29% yield whereas with Boc-protection the desired Boc-Cys(Boc)-OCH=CH_2 (**8t**) was obtained in 87% yield.

Finally, to show the utility of enol esters we subjected vinyl benzoate as model substrate to some follow-up reactions (Scheme 7). At first, the role of enolesters for carboxyl activation in aminolysis reaction was studied. Previous work already in the sixties by Beyerman[2a] and more recently by Birman and Yang[2b] has shown the utility of 1,2,4-triazole as an acylation catalyst using enol esters as the acyl donor. By using a mixture of 1,2,4-triazole/DBU (0.1 equiv) as the catalyst, primary aliphatic amines gave the corresponding amides **9a-c** in high yields. It should be noted that at least 2 equiv of amine is required to trap the liberated acetaldehyde. Although morpholine

served as a suitable nucleophile to give **9d**, the sterically more demanding aliphatic acyclic secondary amines and aniline gave no conversion towards **9e-g**. The same reaction conditions allowed facile transesterification using primary (**10a**, **b**), phenolic (**10c**) and secondary (**10d**, **e**) alcohols, although the latter needed elevated temperatures.[2d] Also here sterics played a role as *t*-BuOH gave no conversion. Aliphatic thiolates served as suitable nucleophiles and gave thioesters **11a**, **b** in high yields. Unexpectedly, phenyl thiolate did not give any reaction. It was found that in the absence of a nucleophile and using a slight excess of the equimolar azole/DBU combination, hemiaminal esters **12a-e** were formed with high efficiency.[11] By using cyanide as the nucleophile, the cyanohydrine ester **13** was obtained albeit in moderate but yet unoptimized yield. Finally, mildly activated vinyl benzoate (**1a**) could be reduced in high yield to benzyl alcohol (**14**) using $NaBH_4$.



Scheme 7. Some enol ester follow-up transformations.

In conclusion, we have developed efficient and scalable CLE-mediated enol esterification methodology of carboxylic acids from alkenyl boroxine pyridine complexes and boronic acids. A wide variety of both aliphatic and aromatic carboxylic acids in combination of all substitution patterns of alkenyl boroxines showed their compatibility. In the case of 2-substituted alkenyl boroxines the double bond configuration was fully retained in the enol ester product. Also N-hydroxyimides, imides and saccharine could be transformed in the respective amidooxy vinyl enol ethers and vinyl enamides. Finally, with the exception of methionine, all other relevant amino acids showed their compatibility to give their enol esters in a stereoselective fashion

Acknowledgements

The authors would like to thank The Netherlands Organization for Scientific Research (NWO-CW, ECHO grant number 711.014.010 to J.v.M). E. Zuidinga and J.M. Ernsting (University of Amsterdam) are acknowledged for mass spectrometry and NMR assistance.

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10.1002/adsc.201800914

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