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Stereo- and Chemoselective Cross-Coupling between Two Electron-Deficient Acrylates: An Efficient Route to (*Z*,*E*)-Muconate Derivatives

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Supporting Information

ABSTRACT: A Ru-catalyzed direct oxidative cross-coupling reaction of acrylates was developed. It offers a straightforward and atom-economical protocol for the synthesis of functionalized (*Z*,*E*)-muconate derivatives in moderate to good yields with good stereo- and chemoselectivities. The conjugated muconates bearing differentiable terminal functionality can be selectively transformed into versatile synthetic intermediates widely used in organic synthesis.

Functional conjugated muconate fragments are versatile building blocks in organic synthesis.[1] Among the methods,[2] a cross-coupling reaction between two different acrylates will provide one of the most straightforward and atom-economical strategies for the synthesis of this class of compounds (Figure 1). Although the oxidative C−H bond alkenylation on alkenes such as simple alkenes,[3] acrylamides,[4] enamides,[5] enolates,[6] and α-oxoketene dithioacetals[7] have been successfully achieved, a direct cross-coupling reaction of easily accessible acrylates via C−H functionalization to generate a functional conjugated muconate is difficult and challenging.[8] This is because homodimerization of alkyl acrylates can easily occur[9] due to the small difference in steric and electronic effects and, therefore, is a major deleterious problem to be circumvented. Furthermore, owing to the intrinsically poor activity of the ester group to coordinate with the metal center,[10] the chelation-assisted alkenylation of acrylate relying on ester as the directing group appears particularly difficult.[11] Recently, an *ortho*-selective Ru-catalyzed oxidative alkenylation of arenes by employing esters as directing groups has been elegantly illustrated by Ackermann et al.[11c] Inspired by our previous observation that substitution at the α-position of alkene was crucial to facilitate the vinylic C(sp^2)−H direct functionalization[3a,b] as well as both Lewis[12] and Murai's[13] seminal works on the use of Ru complexes for C−H activation, we focused on the Ru-catalyzed oxidative coupling[14,15] of α-substituted acrylates to address these issues. Herein, we disclose an unprecedented Ru(II)-catalyzed stereo- and chemoselective cross-coupling reaction of two different acrylates. This process affords a facile synthetic pathway to a number of functionalized muconate derivatives through vinylic C−H bond activation.

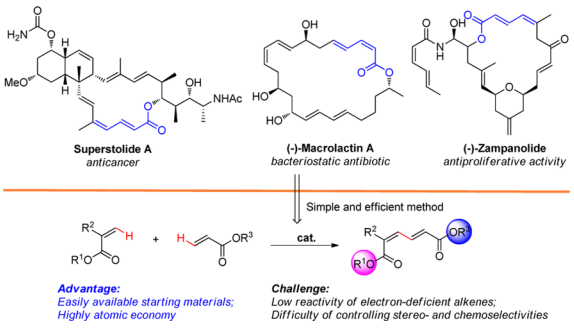

Figure 1. Direct strategy for the synthesis of muconate derivatives.

To evaluate the feasibility of the cross-coupling reaction of acrylates, we chose the commercially available *n*-butyl methacrylate **1a**, an α-substituted acrylate, as a test substrate, together with *n*-butyl acrylate **2a** as the coupling partner. Optimization studies employing inexpensive $[RuCl_2(p\text{-cymene})]_2$ as the catalyst are summarized in Table 1. Notably, the cross-coupling product **3aa** was provided with treatment of **1a** with *n*-butyl acrylate **2a** in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), and $Cu(OAc)_2{\cdot}H_2O$ in 1,2-DCE at 135 °C for 24 h with a 48% isolated yield and 92/8 *Z*,*E*/*E*,*E* ratio (Table 1, entry 1). The *Z*-configuration of product **3aa** was determined by a NOESY NMR spectrum study, implying the involvement of the directing effect of the ester group in the C(sp^2)−C(sp^2) bond formation step in the catalytic cycle.[11c,16] It is worthwhile to mention that a significant amount of homodimerization of **2a** was also produced, consistent with literature reports, and intriguingly, only a trace amount of homocoupling byproduct originating from **1a** was observed. This is likely a result of the steric hindrance to the adjacent vinylic C−H bond. After screening a series of representative solvents, we were pleased to find that the product yield was improved to 67% when the reaction was conducted in a 1,4-dioxane (Table 1, entries 2−5). Employment of acetic acid into the catalytic system was not beneficial for the reaction (Table 1, entries 6−7). Other tunings of the reaction parameters such as the additive and oxidant, also failed to further improve the yield (Table 1, entries 8−11). Moreover, elevation of the temperature (160 °C) led to a remarkable decrease of the reaction selectivity, whereas a lower temperature (100 °C) reduced the reaction efficacy (Table 1, entries 12−13). It was also observed that the yield substantially dropped down with a prolonged reaction time, indicating the instability of the product under the reaction conditions (Table 1, entry 14). For the complete consumption of α-substituted

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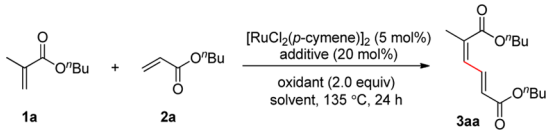
Table 1. Optimization Studies with $[RuCl_2(p\text{-cymene})]_2$ as a Catalyst[a]



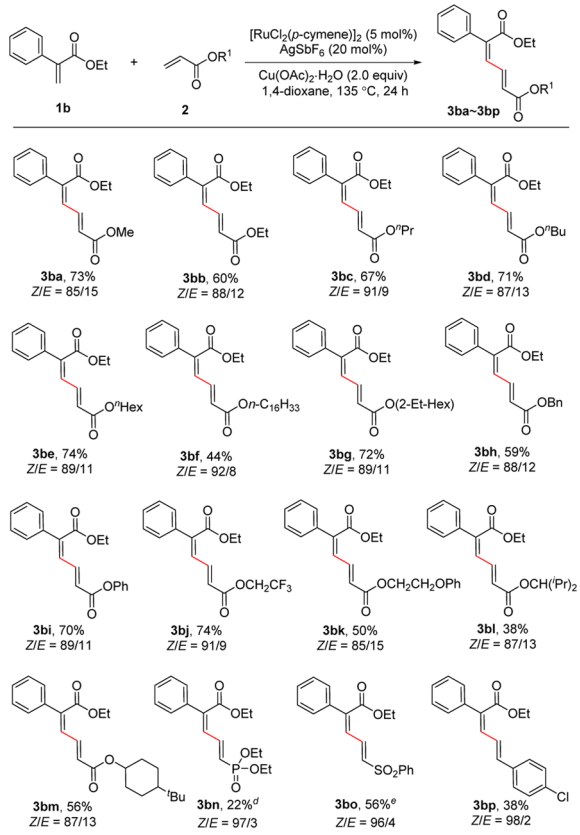
entry	additive	oxidant	solvent	yield (%)	Z/E
1	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	1,2-DCE	48	92/8
2	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	*t*-AmOH	–	–
3	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	toluene	–	–
4	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	DMF	–	–
5	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	1,4-dioxane	67	85/15
6	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	1,4-dioxane/AcOH[b]	52	86/14
7	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	1,4-dioxane	45[c]	86/14
8	KPF_6	$Cu(OAc)_2\cdot H_2O$	1,4-dioxane	<5	–
9	TMBA	$Cu(OAc)_2\cdot H_2O$	1,4-dioxane	<5	–
10	$AgSbF_6$	Ag_2CO_3	1,4-dioxane	–	–
11	$AgSbF_6$	AgOAc	1,4-dioxane	–	–
12	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	1,4-dioxane	39[d]	86/14
13	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	1,4-dioxane	57[e]	62/38
14	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	1,4-dioxane	42[f]	84/16
15	$AgSbF_6$	$Cu(OAc)_2\cdot H_2O$	1,4-dioxane	38[g]	85/15

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), additive (20 mol%), and oxidant (0.4 mmol, 2.0 equiv) in solvent (0.8 mL) at 135 °C for 24 h. Isolated yields. [b]1,4-Dioxane/AcOH = 10/1 (v/v). [c]3.0 equiv of AcOH were added. [d]Reaction at 100 °C. [e]Reaction at 160 °C. [f]The reaction time was prolonged to 48 h. [g]An equimolar amount of **1a** and **2a** was used. 1,2-DCE = 1,2-dichloroethane, TMBA = 2,4,6-trimethylbenzoic acid.

acrylate **1a**, 2 equiv of simple acrylate **2a** were essential (Table 1, entry 15).

After optimization of the reaction conditions, we next examined the scope and limitation of acrylates by employing **1b** as the coupling partner (Table 2). It was found that a wide variety of readily available acrylates **2** bearing alkoxy and aryloxy substituents on the oxygen atom could provide moderate to good yields of the corresponding muconate derivatives successfully. As shown in Table 2, the substitution patterns had little influence on the coupling selectivity. It is interesting to mention that increasing the chain length of the alkoxy moiety (ethyl, propyl, butyl, and hexyl) in acrylates led to the steady improvement of the yield ranging from 60% to 74%, except for the methyl group. The best result was obtained with hexyl acrylate, producing the corresponding 1,4-dienedioate (**3be**) in 74% yield. In addition, stearyl acrylate bearing a long aliphatic side chain was also a capable reactant in this cross-coupling reaction, albeit with a modest yield (**3bf**). Investigation of the electron effect on the acrylates **2** revealed that both electron-withdrawing and -donating groups were applicable for the catalytic system, with the former affording the product in higher yield (**3bj** and **3bk**).

Table 2. Substrate Scope for the Cross-Coupling Reaction of Acrylates[a,b,c]



[a]Conditions: **1b** (0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), and $Cu(OAc)_2\cdot H_2O$ (0.4 mmol, 2.0 equiv) in 1,4-dioxane (0.8 mL) at 135 °C for 24 h. [b]Isolated yields. [c]*Z*/*E* ratios of the isomers were determined by ^1H NMR. [d]56% of **1b** was recovered. [e]1.2 equiv amount of **2** was used.

Nevertheless, when *tert*-butyl acrylate was employed under the applied conditions, no cross-coupling product was observed. Secondary alkoxy substituted acrylates reacted sluggishly, probably arising from the partial decomposition of the starting material under the reaction system (**3bl** and **3bm**). To our satisfaction, other electron-deficient alkenes such as vinyl phosphonate, sulfone, and styrene also proved to be viable coupling partners (**3bn**–**3bp**).[17]

Then, we turned our attention to further expand the scope of the reaction to other aliphatic and aryl substituted acrylates (Table 3). *n*-Butyl methacrylate **1a** reacted with 2,2,2-trifluoroethyl acrylate to give the coupling product **3aj** in 63% yield with 84/16 *Z*/*E* ratio selectivity. Subjecting acrylate **1** tethering a hexyl, phenylpropyl, or cyclopropylmethyl substituent at the α-position to simple acrylate **2** furnished the corresponding cross-coupling muconates in moderate yield but with good selectivity. When a bulkier secondary alkyl group in acrylate **1** was involved in this coupling, higher *Z*-selectivity was observed (up to 98:2) (**3ej** and **3fj**). Notably, introduction of an ester side chain has no effect on the product selectivity (**3gd**). In contrast to the previously observed electronic effect of simple acrylate **2**, an electron-donating group present on the phenyl ring of the α-substituted acrylate **1** proved to accelerate the reaction (**3id** versus **3jd**). It should be noted that the acrylate **2** bearing a bromo substituent was compatible to the current system. The cross-coupling reaction between 1-naphthalenyl acrylate and *n*-

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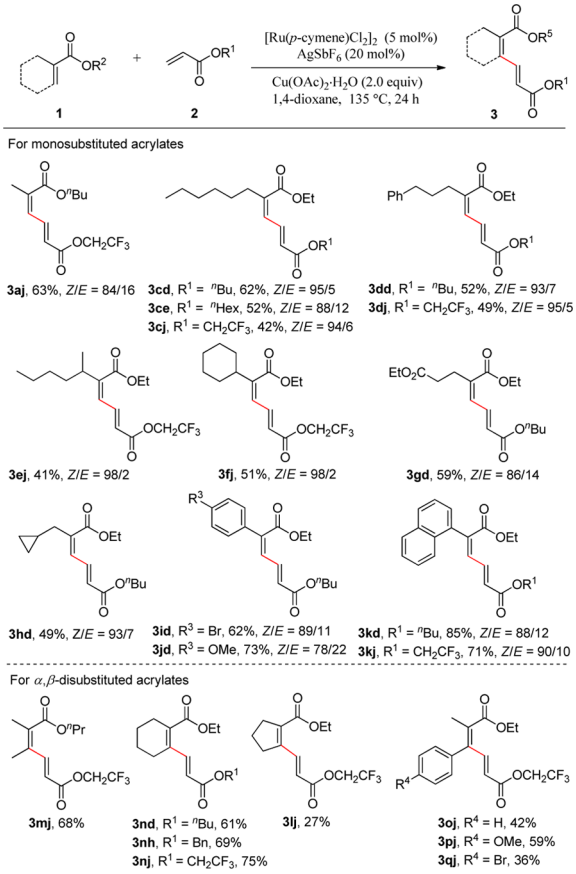
Table 3. Substrate Scope for the Cross-Coupling Reaction of Acrylates[a,b,c]



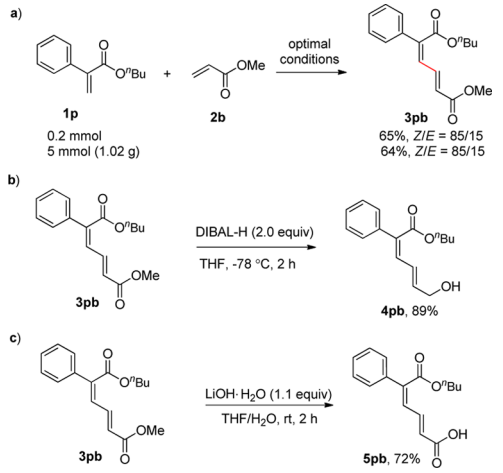
[a]Conditions: **1** (0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), and $Cu(OAc)_2 \cdot H_2O$ (0.4 mmol, 2.0 equiv) in 1,4-dioxane (0.8 mL) at 135 °C for 24 h. [b]Isolated yields. [c]*Z*/*E* ratios of the isomers were determined by ^1H NMR.

butyl or 2,2,2-trifluoroethyl acrylate occurred smoothly to give the corresponding products in 85% and 71% yields, respectively (**3kd** and **3kj**).

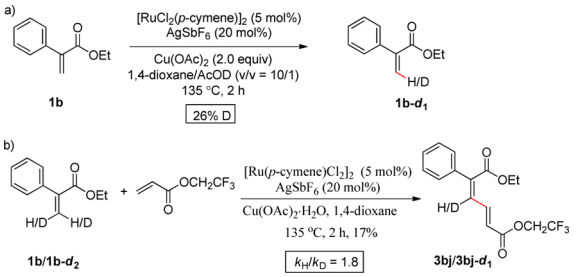
Moreover, this newly developed catalytic protocol is not limited to α-monosubstituted acrylates but is also applicable to α,β-disubstituted acrylate derivatives, in which case the cross-coupling products were accompanied in a highly regiocontrolled manner under the optimal reaction conditions. Acrylates **1** embedded with a cyclohexenyl moiety reacted with a series of simple acrylates **2** affording the desired products in good yields (**3nd**, **3nh**, and **3nj**). However, an acrylate bearing a cyclopentenyl unit showed lower reactivity along with a low conversion (**3lj**). When α-alkyl-β-aryl substituted acrylates were subjected to the reaction conditions, the corresponding products were isolated in 36−59% yields (**3oj**, **3pj**, and **3qj**) wherein the results showed the same electronic effect as the α-aryl substituted acrylates. β-Substituted acrylate, as exemplified with (*E*)-ethyl cinnamate, was also tested in this catalytic system; however, low conversion was observed.

Under the optimal conditions, the cross-coupling reaction can be scaled up to 5 mmol without a decrease in yield and selectivity, as illustrated by the preparation of product **3pb** to realize the robustness of this strategy (Scheme 1a). Meanwhile, in order to facilitate its potential transformation in the expedient synthesis of complex molecules, we became interested in the selective

Scheme 1. (a) Gram-Scale Synthesis; (b) Selective Reduction; (c) Selective Hydrolysis



Scheme 2. Isotopically Labelled Experiments for KIE Studies



reduction of muconates to differentiate these two terminal ester groups (Scheme 1b). After screening a series of reductants and solvents,[18] we were pleased to find that the methyl ester group could be selectively reduced to the corresponding alcohol **4pb** by DIBAL-H in THF at −78 °C in high yield, with the *n*-butyl ester group intact. Additionally, selective hydrolysis mediated by LiOH successfully afforded the desired monocarboxylic acid **5pb**, which could be further converted into a muconic acid and adipic acid analogue of potential industrial importance (Scheme 1c).[19]

Having demonstrated the versatility of the resultant products, we attempted to gain some preliminary understanding of this reaction mechanism. Upon treatment of phenyl acrylate **1b** with isotopically labeled experiments, a remarkable *Z*-selective olefinic H/D exchange[20] was found in the absence of simple acrylate **2** with the addition of deuterated acetic acid, thereby implicating reversible cyclometalation modes (Scheme 2a).[21] In addition, an intermolecular KIE for the cross-coupling reaction of acrylates was determined to be k_H/k_D = 1.8. This indicates that the C(sp^2)−H bond cleavage should be involved in the rate-determining step of the catalytic cycle.[22] The H/D exchange of simple acrylate was not observed possibly due to the reactivity difference between the α-substituted acrylate and simple acrylate caused by the electronic effect (Scheme 2b).

In conclusion, we have developed an efficient Ru-catalyzed cross-coupling reaction of acrylates, which provides a rapid and atom-economical route to a variety of highly functionalized (*Z*,*E*)-muconate derivatives. The coordination of the Ru complex with the weakly directing ester group is critical for high stereoselectivity in this transformation. The substituent on the α-position of acrylate influences its reactivity and chemoselectivity. It is worth noting that in contrast with the *E*,*E*

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configuration of conjugated dienes which can be synthesized from the coupling reaction of alkenes with alkynes[23] or allenes[24] by a mechanistically different approach, this established strategy opens up a complementary route to multisubstituted (*Z*,*E*)-1,3-diene motifs. More importantly, the crossing products can be obtained on a preparative scale and selectively transformed into valuable butadienes that could be served as useful building blocks for natural products syntheses. Considering the versatile utilities of muconates, we expect that this reaction may become a powerful and general synthetic protocol in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data of new compounds, transformation of muconate, deuterium exchange, kinetic isotope effect experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) The use of vinyl methyl ketone and acrylonitrile under the optimized conditions only provided a trace amount of cross-coupling product with the starting material being recovered.

(18) Other reductants such as $LiAlH_4$ and $NaBH_4$ led to the reduction of the conjugated double bond of compound **3pb**. The solvent THF turned out to be crucial, compared with other solvents such as hexane, DCM, and toluene.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Tables 1−3 have been corrected. The paper was re-posted on February 4, 2015.

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