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Diversity-Oriented Syntheses: Coupling Reactions Between Electron-Deficient Olefins and Aryl Aldehydes via C(sp^2)−H Functionalization

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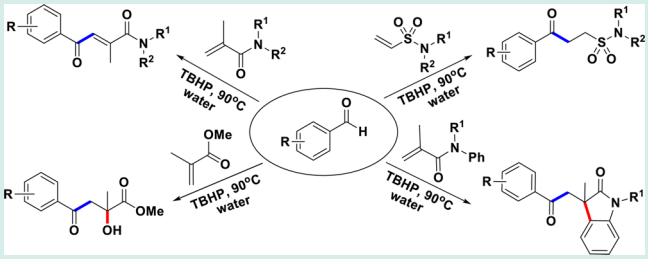
Supporting Information

ABSTRACT: A diversity-oriented syntheses by coupling three electron-deficient olefins (vinyl sulfonamides, methacrylamides, and methyl acrylates, respectively) with aryl aldehydes via C(sp^2)−H functionalization were reported. These reactions gave four different skeletal products respectively under environment-friendly and mild conditions. All these reactions are highly regioselective and effective, very suitable for the preparation of synthetic building blocks and compound library, the results will enrich current coupling chemistry of olefins with aldehydes and can be applied to other chemistry areas as well.

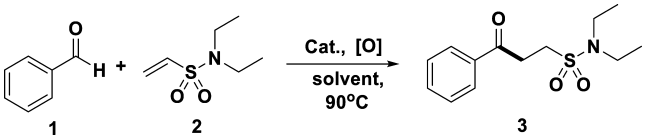


KEYWORDS: *diversity-oriented synthesis, C(sp^2)−H functionalization, environmentally friendly, regioselective, olefin, aldehydes*

The oxidative cross coupling of activated aldehyde Csp^2−H bonds with another Csp^2−H bond has attracted a lot of recent attention,[1] because these reactions involve C(sp^2)−H functionalization. They generate versatile synthetic substrates which are very useful for the preparation of natural products and compound library.[2] Normally these reactions are atom-economic and highly efficient.[3] The coupling reaction between olefins and aldehydes is especially desirable and valuable for forming carbon−carbon bonds important for constructing molecular skeletons and synthetic building blocks,[4] due to the ready availability of both reagents, especially aldehydes. Recently, some progress in this quest has been achieved, where aldehyde C(O)−H bonds have been activated for coupling reactions with electron-rich olefins Csp^2−H bonds to afford ketones.[5] Despite this initial progresses,[6] reactions of electron-deficient olefins with the aldehyde C(sp^2)−H bonds have great potential for further development of space and exploration.

Reports exist where aldehydes and electron-rich phenyl-substituted electron-rich olefins were used for oxidative coupling reactions.[7] However, only a couple of reports of coupling reactions between aldehydes and electron-deficient olefins were reported.[5a,b] We have recently communicated an initial report of cascade cross coupling via C(sp^2)−H functionalization to form carbon−carbon bonds from aldehydes and electron-deficient methacrylamides.[7c] We now expand this chemistry by using another two electron-deficient olefins (vinyl sulfonamides and methacrylates), and different unexpected structures of products are obtained in good yields.

Table 1. Oxidative Coupling of *N*,*N*-Diethyl Vinyl Sulfonamide with Benzaldehyde[a]



1 2 3

entry	catalyst (mol %)	oxidant	solvent	reaction time (h)	yield (%)[b]
1	$CuBr_2$ (20)	O_2		10	
2	CuO (20)	TBHP		10	70
3	CuI (20)	TBHP		10	trace
4	$CuCl_2$ (20)	TBHP	DCE	10	trace
5	$CuCl_2$ (20)	TBHP	dioxane	10	trace
6	$CuCl_2$ (20)	TBHP	toluene	10	10
7	$CuCl_2$ (20)	TBHP	CH_3CN	10	trace
8	$CuCl_2$ (20)	TBHP	DMF	10	trace
9	$CuCl_2$ (10)	TBHP		10	65
10	$CuCl_2$ (20)	DTBP		10	
11	$CuCl_2$ (20)	TBHP		10	73
12	$CuCl_2$ (20)	DTBP		10	
13		TBHP		10	70

[a]Reaction conditions: benzaldehyde (3.5 equiv), vinyl sulfonamide (1 equiv), aqueous TBHP [*tert*-butyl hydroperoxide 70 wt % in water (2.5 equiv)], copper catalyst (10 mol %, or 20 mol % of **2a**). [b]Isolated yield is based on reactant **2a**, DTBP = *di-tert*-butyl peroxide.

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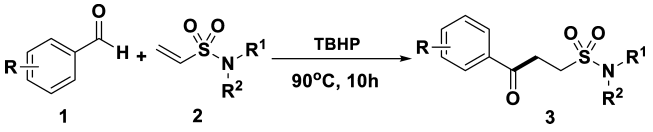
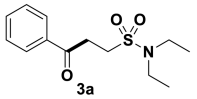
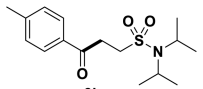
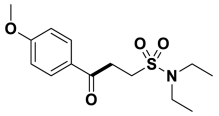
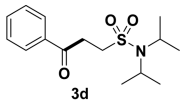
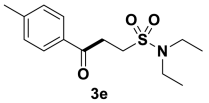
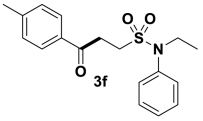
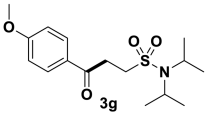
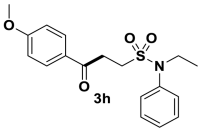
Table 2. Addition of Aromatic Aldehydes to N,N-Disubstituted Vinyl Sulfonamides via C(sp^2)−H Functionalization[a]



1 2 3

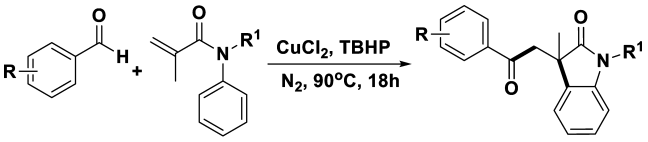
entry	R	R^1	R^2	product	yield %[b]
1	H	Et	Et	 3a	68
2	4-Me	*i*-Pr	*i*-Pr	 3b	72
3	4-MeO	Et	Et	 3c	76
4	H	*i*-Pr	*i*-Pr	 3d	65
5	4-Me	Et	Et	 3e	73
6	4-Me	Et	Ph	 3f	68
7	4-MeO	*i*-Pr	*i*-Pr	 3g	70
8	4-MeO	Et	Ph	 3h	75

[a]Reaction conditions: benzaldehyde (3.5 equiv), vinyl sulfonamide (1 equiv), aqueous TBHP [*tert*-butyl hydroperoxide 70 wt % in water (2.5 equiv)]. [b]Isolated yield is based on reactant **2**.

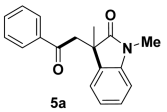
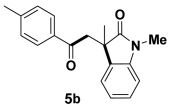
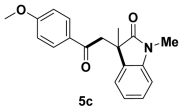
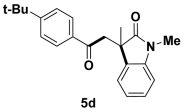
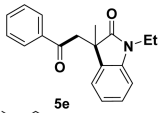
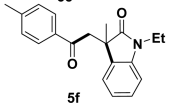
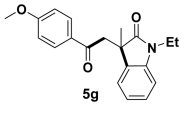
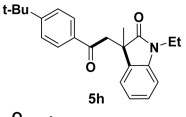
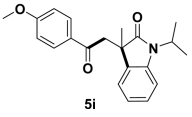
Reaction conditions were screened to search for suitable oxidative coupling results between the electron-deficient olefins and aryl aldehydes. Benzaldehyde and *N*,*N*-diethyl vinyl sulfonamide were selected as representative reactants for screening, and various catalysts, solvents, reaction times (h) and yields were screened. On the basis of previous research,[8] metal catalyst screening focused mainly on copper systems which had proved to be good for promoting oxidative coupling of aldehydes with other nucleophiles or aromatic Csp^2−H bonds to form new C−C bonds.[9] But some reactions without metal catalysts were also screened. Example screening results are presented in Table 1.

Screening reactions between benzaldehyde and *N*,*N*-diethyl vinyl sulfonamide[10] (Table 1), demonstrated that excess benzaldehyde (3.5 equiv) and aqueous TBHP (2.5 equiv, 70% in water as an oxidant) promoted conversion to *N*,*N*-diethyl-3-oxo-phenylpropyl-1-sulfonamide **3a**. When $CuBr_2$ or

Table 3. Oxidative Cross Coupling Cascade Reactions of *N*-alkyl-*N*-phenylmethacrylamide 4a−c with Aryl Aldehydes[a]

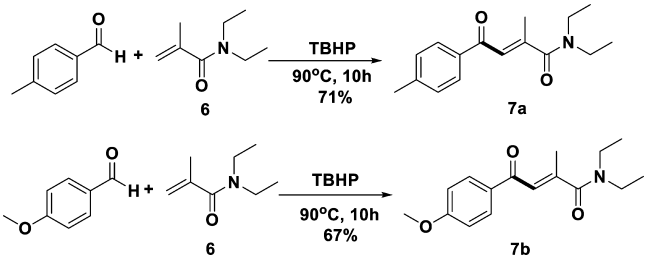


4 5a-i

entry	R	R^1	product	yield (%)[b]
1	H	Me	 5a	70
2	4-Me	Me	 5b	72
3	4-MeO	Me	 5c	62
4	4-*t*-Bu	Me	 5d	86
5	H	Et	 5e	70
6	4-Me	Et	 5f	69
7	4-MeO	Et	 5g	64
8	*4-t*-Bu	Et	 5h	84
9	4-MeO	*i*-Pr	 5i	80

[a]Reaction conditions: aldehyde (3.5 equiv), *N*-alkyl-*N*-phenylacrylamide (1 equiv), aqueous TBHP (70 wt % in water, 2.5 equiv), copper catalyst (20 mol % of **4a−c**). [b]Isolated yield is based on reactant **4**

Scheme 1. Oxidative Coupling of *N*,*N*-Diethylmethacrylamide 6 with Aryl Aldehydes



6 7a 6 7b

CuI, (20% mol) were used as catalysts in the absence of solvent (entries 1, 3), none or only trace amounts of product **3a** was

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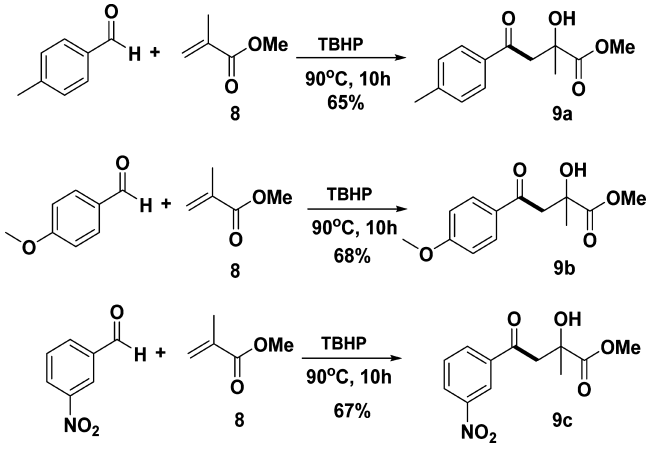
Scheme 2. Oxidative Cross Coupling of Methyl Methacrylate with Aryl Aldehydes

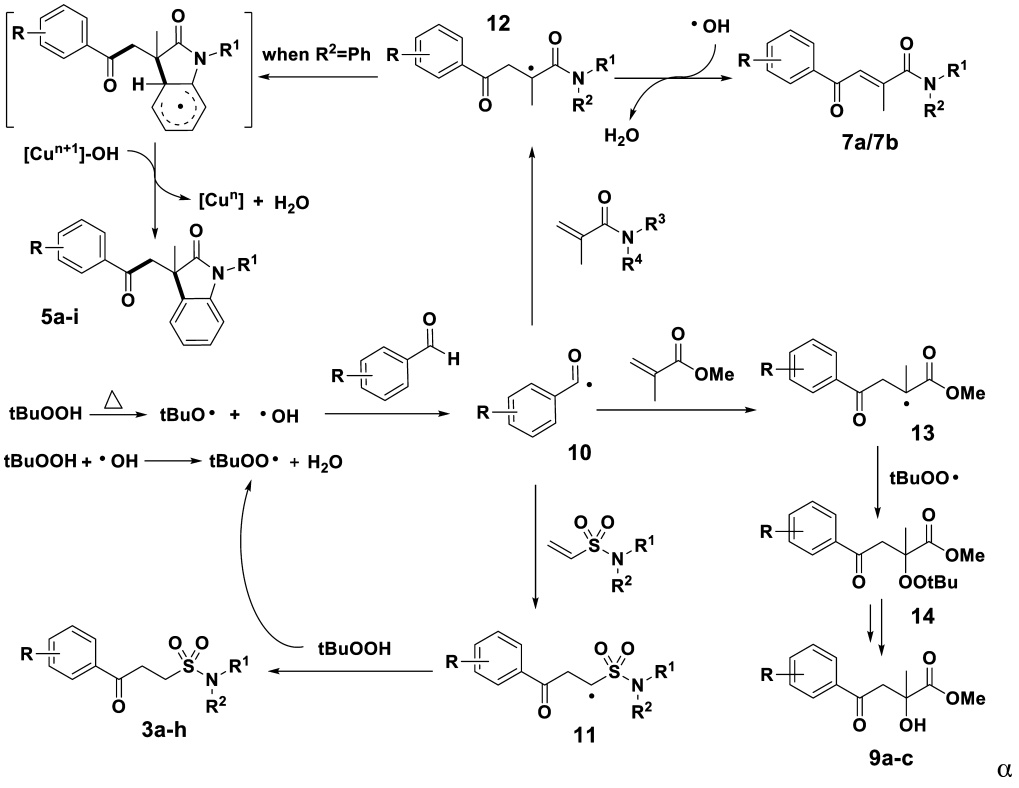


detected. Surprisingly, using CuO gave about 70% yields of **3a**. Using DCE, dioxane, CH_3CN or DMF as solvents (entries 4, 5, 7, 8) with $CuCl_2$ as a catalyst did not afford any **3a** or only produced trace amounts of this product. In toluene (entry 6), the reaction generated only a 10% yield of **3a**. Employing $CuCl_2$ (10% mol) in the absence of organic solvent (entry 9) unexpectedly gave **3a** in 65% yield after 10 h. Increasing the amount of $CuCl_2$ to 20% mol without solvent (entry 11) increased the yield of **3a** to 73%. When no catalyst was used, the reaction still proceeded well. After 18 h, a 70% yield was observed. On the basis of the screening results, we found the reactions with $CuCl_2$ as a catalyst were not different from the ones without $CuCl_2$ catalyst, so both reaction conditions were used respectively for the following coupling reactions.

Eight couplings with different vinyl sulfonamides were investigated at the selected conditions. All gave *N,N*-dialkyl-3-oxo-3-arylpropyl-1-sulfonamides in good yields (Table 2). The coupling chemistry between electron-deficient vinyl sulfonamides and aldehydes was extended to methacrylamides. Interestingly, when the vinyl sulfonamides were replaced by *N*-alkyl-*N*-phenylamide groups, the couplings proceeded as cascade reaction sequences where initial Csp^2–H/Csp^2–H coupling was followed by intramolecular cyclization. Instead of giving linear skeletal products analogous to **3a**–**h**, these cascade reactions gave ketone oxindole derivatives **5a**–**i** in moderate yields (Table 3). The electron-withdrawing 2-nitrobenzaldehyde was also tried for the reactions with *N,N*-diethyl vinyl sulfonamide and *N*-methyl-*N*-phenylmethacrylamide as described in Tables 2 and 3, respectively, but we found that both reactions did not proceed well affording low yields of corresponding products.

When *N*-alkyl-*N*-phenylamide group of methacrylamide **4** was replaced by *N,N*-dialkyl amide group, this coupling reaction could not undergo cascade cyclizations. Instead, linear coupling occurred similar to that with the *N,N*-disubstituted vinyl sulfonamides. However, the original methacrylamide double bond was still retained in each of the coupling products when *N,N*-dialkylamides were employed (Scheme 1). Here *N,N*-dialkyl methacrylamide was used as a representative reactant. Both *p*-methylbenzaldehyde and *p*-methoxybenzaldehyde reacted well with *N,N*-diethyl methacrylamide, respectively, to give *N,N*-diethyl-2-methyl-4-oxo-4-arylbut-2-enamides **7a**, **7b** in good yields.(Scheme 1)

Scheme 3. Proposed Reaction Mechanisms for the Couplings of Vinyl Sulfonamides, Methacrylamides, and Methacrylates with Aryl Aldehydes



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These couplings were further extended to using methyl methacrylate as the electron-deficient reactant. Methacrylate is a representative electron-deficient ester, *p*-methylbenzaldehyde, *p*-methoxybenzaldehyde and *m*-nitrobenzaldehyde were employed as representative aryl aldehydes to react with methyl methacrylate (Scheme 2). In the absence of metal catalysts, these coupling reactions proceeded well to give good yields of corresponding products **9a**−**c** in aqueous TBHP. These reaction products differ from the couplings shown in Scheme 1, because they do not retain the electron-deficient double bond as found in coupling products of **7a**−**b**. Instead, a single carbon−carbon bond exists at this position, ^{1}H NMR and mass spectroscopy verified that there is an OH function present in these products. This was also confirmed by IR analysis, which showed a strong absorption at 3200−3400 cm^{-1}, indicating the existence of an OH group at the α-positions of **9a**−**c** ester functions.

How do these three different but similar electron-deficient olefin substrates (vinyl sulfonamides, methacrylamides and methacrylates) generate three different types of products? On the basis of previous reports and these new results, a reaction mechanism consistent with the products is proposed in Scheme 3. First TBHP is split by heating to give *t*-BuO$^\bullet$ and HO$^\bullet$ radicals, which can also abstract hydrogen from *t*-BuOOH to give *t*-BuOO$^\bullet$ radical. The *t*-BuO$^\bullet$ radical abstracts hydrogen from the aryl aldehyde to generate the acyl radical. The acyl radical adds to the β-position of the double bond of vinyl sufonamides to give radical intermediate **11**, which subsequently abstracts a hydrogen atom from *t*-BuOOH to give product **3a**−**h**. With methacrylamides, the acyl radical adds to the electron-deficient olefin to generate intermediate radical **12**. This loses a hydrogen atom at the amide's β-position to give *N*,*N*-diethyl-2-methyl-4-oxo-4-arylbut-2-enamides **7a**/**7b**. When R^2 is aryl, the intermediate radical **12** attacks the aryl ring of aniline substrate, followed by the abstraction of aryl hydrogen by TBHP to give products **5a**−**i** in moderate yields. The intermediate radical **13** from methyl methacrylate combines with a *t*-BuOO$^\bullet$ radical from TBHP to give intermediate **14**, which undergo subsequent reduction through O−O bond cleavage to give the α-hydroxy ester **9a**−**c** in good yield. The radical **12** could take the same route as radical **13**, dehydration of the analogous α-hydroxy product from **12** under driving reaction conditions could also provide **7a**/**b**. The reason why the three intermediate radicals **11**, **12**, **13** took different reaction routes may be related to their lifetimes and reactivity.

In summary, a diversity-oriented syntheses by coupling three electron-deficient olefins (vinyl sulfonamides, methacrylamides and methyl acrylates, respectively) with aryl aldehydes via C(sp^2)−H functionalization were reported. These three reactions gave four different skeletal products, all these reactions are atom-economical, effective and highly selective, These results have enriched the coupling chemistry of olefins with aldehydes, providing more green and powerful strategies for the syntheses of molecular building blocks which can be used for compound library production and syntheses of different pharmaceutical molecules in the future.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and spectral characterization for all compounds. 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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