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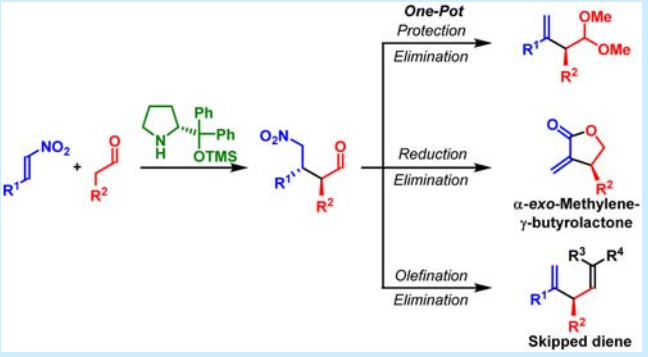
Formal Asymmetric α-Alkenylation of Aldehydes and the Synthetic Application toward Forming α-*exo*-Methylene-γ-butyrolactones and Skipped Dienes

Yang Li, Lise Ibsen, and Karl Anker Jørgensen*

Department of Chemistry, Aarhus University, Langelandsgade 140, DK-8000 Aarhus C, Denmark

Supporting Information

ABSTRACT: A formal asymmetric α-alkenylation of aldehydes is reported based on the organocatalytic reaction of aldehydes with nitroacrylates. The reaction proceeds in a one-pot manner forming the products with up to 77% yield and up to >99% ee. This strategy is also successfully applied for the synthesis of α-*exo*-methylene-γ-butyrolactones and skipped diene scaffolds in a highly enantioselective manner.

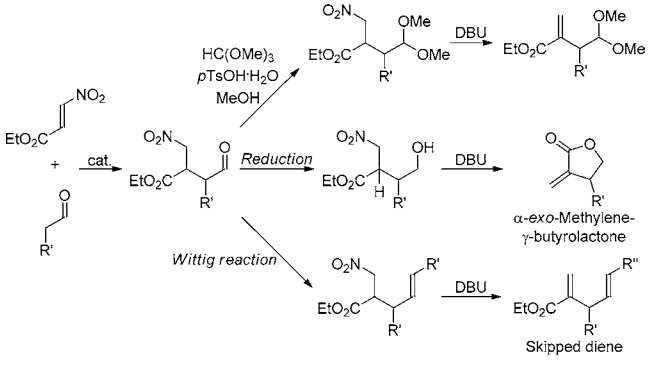


Asymmetric α-alkenylation of carbonyl compounds is a useful, but challenging, transformation in organic synthesis that has received a lot of attention. It has been shown that by using chiral auxiliaries aldehydes and ketones can be converted into β,γ-unsaturated carbonyl compounds with high enantioselective control through multiple steps.[1] More recently, several novel strategies have been shown to install the alkenyl group directly at the α-position of carbonyl compounds. The Buchwald group has described such an approach by a coupling reaction between ketone enolates and vinyl bromides applying palladium catalysis.[2] Fu et al. have developed nickel-catalyzed alkenylation of α-halo carbonyl compound.[3] Phase-transfer catalysis has also been applied to install a double bond at the α-position of 1,3-dicarbonyl compounds.[4] In 2008, enantioselective α-alkenylation of aldehyde was achieved by organo-SOMO catalysis by MacMillan's group, and they also expanded the strategy to synergistic combination of copper and aminocatalysis in the following years.[5] To the best of our knowledge, these are the only examples of direct enantioselective α-alkenylation of carbonyl compounds. Recently, Maruoka et al. demonstrated a binaphthyl-modified chiral amine catalyzed conjugated addition of aldehyde to β-tosyl enones.[6] In this work, the tosyl group was eliminated to a double bond, providing the product of a formal α-alkenylation of aldehydes. It is notable that, in most of the cases, the installed double bond in the product is internal, while generation of a terminal double bond is less developed.

Organocatalytic reactions between aldehydes and nitroolefins have been thoroughly studied,[7] and it has been shown that the nitro group can be eliminated under suitable reaction conditions.[8] We envisioned that it should be possible to install the alkenyl group at the α-position of the aldehyde through an addition−elimination reaction sequence.

To our delight, the reaction was performed successfully by applying ethyl (*E*)-3-nitroacrylate[7h,l−n,9] as the alkene source. DBU was used as the base to promote the elimination of nitrous acid. Protection is needed before the elimination, and all three steps are performed in a one-pot manner (Scheme 1, top). Moreover, the product contains a terminal double bond, which is not very common in previous works. The protection step can be performed in several ways, which will lead to different useful products. We envisioned that a reduction, or a Wittig reaction, can be performed after the catalytic step. By

Scheme 1. Formal α-Alkenylation Reaction of Aldehyde and Planned One-Pot Reactions Based on the Organocatalytic Reaction of Aldehydes with Nitroacrylates



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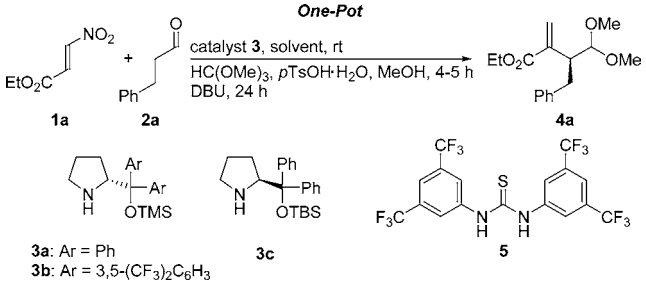
treating the resulting intermediates with base, α-*exo*-methylene-γ-butyrolactone[10] and skipped diene[11] scaffold can be obtained, respectively (Scheme 1, middle and bottom). It is notable that these motifs are present in a vast array of natural products with diverse useful biological activities; however, the available catalytic asymmetric synthetic method approaching these scaffolds remains limited.[12] Herein, we report the formal α-alkenylation of aldehydes and the synthetic application toward forming α-*exo*-methylene-γ-butyrolactones and skipped dienes in a highly enantioselective manner based on organocatalysis and simple transformations (Scheme 1).

Studies were initiated by using ethyl (*E*)-3-nitroacrylate **1a** and 3-phenylpropanal **2a** as standard compounds, and a screening of reaction conditions for the first step of the organocatalytic elimination was performed (Table 1). The reaction took place in the presence of catalyst **3a**. It took 2 d to reach full conversion at room temperature (rt) in toluene as the solvent and product **4a** were obtained with 94% ee (Table 1, entry 1). Two other silyl-protected prolinol catalysts were also tested. The catalyst with the 3,5-bis(trifluoromethyl)phenyl group (**3b**) turned out to be inactive (entry 2), while the one with the *tert*-butyldimethylsilyl group (**3c**) increased the reaction time to 3 d without improving the enantioselectivity (entry 3). In order to decrease the reaction time, benzoic acid and hydrogen-bonding catalyst **5** were tested as additives. Both reactions reached more than 95% conversion within 1 d, but the enantioselectivity dropped to 46% ee and 88% ee, respectively (entries 4 and 5). When **5** was used as the additive, the enantioselectivity was improved by lowering the temperature, but the reaction took the same amount of time (compare to entry 1); however, a slightly lower enantioselectivity was obtained (entry 6). The outcome of the reaction is solvent dependent. In THF, the reaction proceeded sluggishly, and only 35% conversion was reached after 2 d (entry 7). The reaction was accomplished within 15 h in both CH_2Cl_2 and $CHCl_3$, and the high enantioselectivity (90% ee) was maintained in $CHCl_3$, while it was reduced to 86% ee in CH_2Cl_2 (entries 8 and 9). To our delight, the reaction proceeded quickly (full conversion within 17 h) at 4 °C in $CHCl_3$ and the enantioselectivity improved to 95% ee (entry 10).

Having the best reaction conditions in hand, the scope of the substrates was evaluated (Scheme 2). First, different nitroacrylates were reacted with 3-phenylpropanal **2a**. Ethyl (*E*)-3-nitroacrylate **1a** provided product **4a** in 77% yield and 93% ee. By using methyl (*E*)-3-nitroacrylate and isopropyl (*E*)-3-nitroacrylate, products **4b** and **4c** were isolated in 59% and 63% yield, 93% ee and 90% ee, respectively.[13] When benzyl (*E*)-3-nitroacrylate was applied, product **4d** was obtained with 75% yield and a lower enantioselectivity (80% ee).

Next, a variety of aldehydes were evaluated by reaction with ethyl (*E*)-3-nitroacrylate **1a**. It was found that both electron-rich and electron-poor substituents at the *para*-position of the phenyl group on 3-phenylpropanal were tolerated, furnishing the corresponding products **4e** and **4f** with good yields and high enantioselectivities, 90% ee and 84% ee, respectively. The aldehyde with a phenylalkynyl group, 5-phenylpent-4-ynal, was also tolerated, even though a lower enantioselectivity was observed (**4g**). When 4-phenylbutanal was applied, product **4h** was obtained with good yield and an excellent enantioselectivity

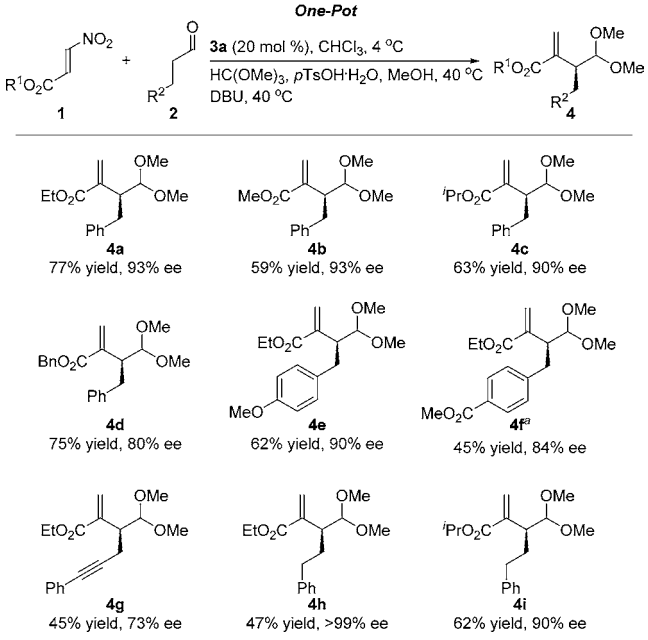
Table 1. Screening Results[a]



entry	catalyst	additive[b]	solvent	time[c] (h)	conv[d] (%)	ee[e] (%)
1	**3a**		toluene	47	>99	94
2	**3b**		toluene	46	<1	
3	**3c**		toluene	72	>99	−86
4	**3a**	BA[f]	toluene	22	96	46
5	**3a**	**5**[g]	toluene	20	>99	88
6[h]	**3a**	**5**[g]	toluene	47	95	92
7	**3a**		THF	46	35	
8	**3a**		CH_2Cl_2	15	>99	86
9	**3a**		$CHCl_3$	15	>99	90
10[h]	**3a**		$CHCl_3$	17	>99	95

[a]All reactions were performed using **1a** (0.075 mmol), **2a** (0.05 mmol), 20 mol % of catalyst, and 0.2 mL of solvent for the first step; 0.25 mL of MeOH, $HC(OMe)_3$ (0.1 mmol), and $pTsOH·H_2O$ (0.015 mmol) were used for the second step; DBU (0.1 mmol) was used for the third step. Steps 2 and 3 were both carried out at 40 °C. [b]The amount of additive is 20 mol %. [c]Reaction time of the first step. [d]Conversion of the first step was measured by ^1H NMR spectroscopy of the crude mixture. [e]The ee determination was carried out by chiral UPC². [f]BA: benzoic acid. [g]**5**: 1,3-bis(3,5-bis(trifluoromethyl)phenyl)-thiourea. [h]Reaction temperature: 4 °C; in step 3, 3.0 equiv of DBU (0.15 mmol) was added.

Scheme 2. Scope of Formal α-Alkenylation of Aldehydes*



*Reaction conditions: **1** (0.15 mmol), **2** (0.1 mmol), **3a** (0.02 mmol), and 0.4 mL of $CHCl_3$ for the first step; 0.5 mL of MeOH, $HC(OMe)_3$ (0.2 mmol) and $pTsOH·H_2O$ (0.03 mmol) for the second step; DBU (0.3 mmol) for the third step. The ee determination was carried out by chiral UPC². [a]The ee was determined by converting **4f** into the corresponding alcohol.

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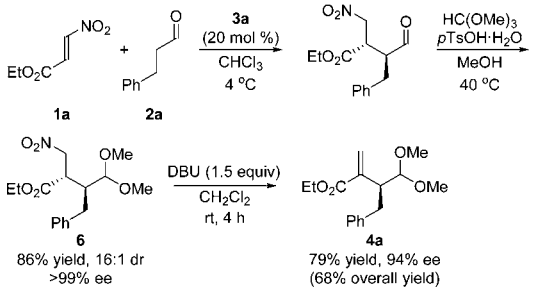
(>99% ee). Finally, 4-phenylbutanal was applied for the reaction with isopropyl (*E*)-3-nitroacrylate, providing a high yield and enantiomeric excess of **4i**.[14]

In order to obtain better insight into this reaction, the reaction was performed in a stepwise manner (Scheme 3). The

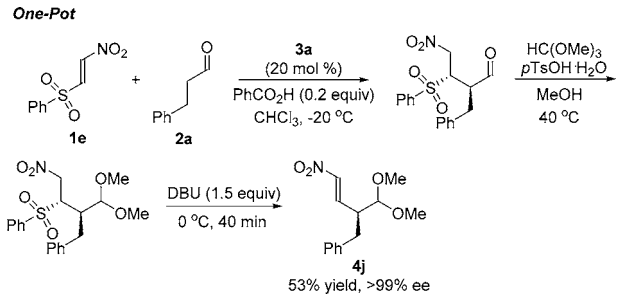
Scheme 3. Stepwise Approach to the Formal α-Alkenylation of Aldehydes



intermediate **6** was isolated in 86% yield, 16:1 dr, and >99% ee.[15] The elimination step was then carried out in CH_2Cl_2 at rt, and product **4a** was obtained in 79% yield (68% overall yield) and 94% ee. The results are comparable with the one-pot procedure. Another observation is that the enantiomeric excess decreased after the elimination step. This indicates that DBU might be able to deprotonate the stereocenter in the product. The ideal base should thus have the following properties: basic enough to promote the elimination of the nitro group but not so basic that it reduces the enantioselectivity. A number of bases have been tested under one-pot reaction conditions, and DBU was found to be the best choice.[16]

To our delight, (*E*)-((2-nitrovinyl)sulfonyl)benzene **1e** can also be applied to this reaction in a one-pot manner (Scheme 4). The catalytic reaction (the first step) was carried out at −20

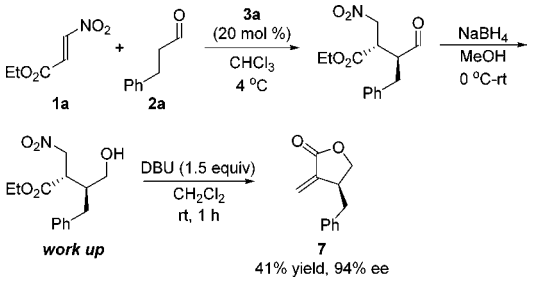
Scheme 4. Formal α-Alkenylation of Aldehydes with Substrate 1e



°C with benzoic acid as additive. The elimination step proceeded efficiently at 0 °C. In this case, the sulfonyl group was eliminated, and product **4j** was obtained with high yield (53%) and excellent enantioselectivity (>99% ee). It shows that an internal alkenyl group can be installed to the α-position of the aldehyde.

We have also applied the methodology for the synthesis of different interesting scaffolds, such as α-*exo*-methylene-γ-butyrolactones and skipped dienes (Scheme 1). As shown in Scheme 5, after the standard catalytic reaction step, a reduction was carried out in a one-pot manner. After the workup, the crude intermediate was directly treated with DBU in CH_2Cl_2 providing the α-*exo*-methylene-γ-butyrolactone **7** in 41% overall

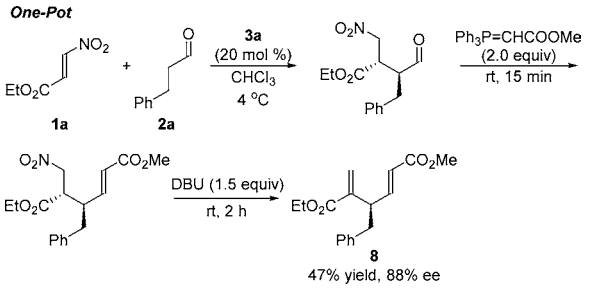
Scheme 5. Synthesis of the α-*exo*-Methylene-γ-butyrolactone 7



yield and 94% ee, along with transesterification and elimination of the nitro group.

In order to generate the skipped diene scaffold, two different transformations were applied. When a Wittig reaction to transform the aldehyde intermediate was applied, the three-step reaction could be performed in one-pot fashion, as described in Scheme 6. The elimination step was performed at rt, and the

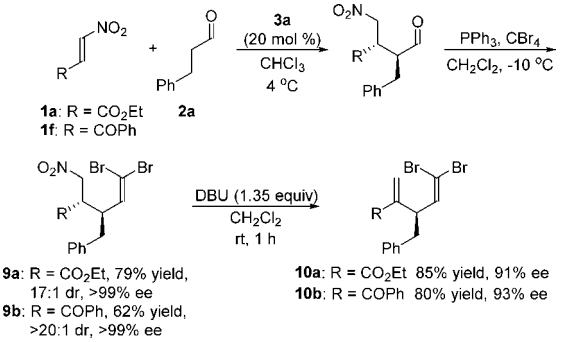
Scheme 6. Synthesis of the Skipped Diene 8



skipped diene **8** was obtained with 47% yield and 88% ee. It is notable that the amount of the DBU is important since a double-bond migration in **8** was observed when more than 1.5 equiv of DBU was added.

In Scheme 7, the Ramirez olefination was applied to transform the aldehyde intermediate to the first alkene **9**. In

Scheme 7. Synthesis of the Skipped Diene 10 and the Application of the Substrate 1f



this transformation, besides the standard nitroacrylate **1a**, (*E*)-3-nitro-1-phenylprop-2-en-1-one **1f** was also successfully applied. The intermediates **9a** and **9b** were obtained in high yield and excellent stereoselectivities. Finally, the elimination step provided products **10a** and **10b** in high yields, 85% and 80% respectively, and high enantioselectivities, 91% ee and 93% ee, respectively.[17] The absolute configuration of these

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compounds was determined according to previous studies.[7f,h,m,n]

In conclusion, an enantioselective formal α-alkenylation of aldehydes is presented based on the aminocatalysis between aldehydes and nitroacrylates in a one-pot manner. A nitroolefin substrate with a sulfonyl substituent was also successfully applied in this reaction. The products are formed in high yields and enatioselectivities (up to 77% yield and up to >99% ee). This strategy has been expanded for the construction of bioattractive scaffolds, such as α-*exo*-methylene-γ-butyrolactones and skipped dienes. In the synthesis of the skipped diene, a nitroolefin substrate with a ketone substituent is also favorable. These scaffolds are synthesized in a highly enantioselective manner with >90% ee.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00254.

Experimental details; ^{1}H and ^{13}C NMR spectra; UPC^2 trace (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kaj@chem.au.dk.

ORCID

Karl Anker Jørgensen: 0000-0002-3482-6236

Notes

The authors declare no competing financial interest.

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(13) The reaction providing **4c** has been performed on a 1 mmol scale (following the same procedure as for the 0.1 mmol scale) with the following results: 84% yield and 93% ee.

(14) Examples with aliphatic aldehydes as substrates are not included due to the unsuccessful enantiomeric excess determination.

(15) The isolation of the intermediate observed after the first step was not successful. The dr value decreased to 4:1 after the fast chromatography, while 17:1 dr was observed from the crude product.

(16) See the Supporting Information for more details.

(17) Enantiomeric excesses of **10a** and **10b** were determined after simple transformations. See the Supporting Information for more details.

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