

N-Heterocyclic Carbene Catalyzed Homoenolate-Addition Reaction of Enals and Nitroalkenes: Asymmetric Synthesis of 5-Carbon-Synthon δ -Nitroesters**

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Judging by recent trends, N-heterocyclic carbene (NHC) catalyzed generation of reactive homoenolate intermediates from enals and the involvement of such intermediates in reactions with a variety of Michael acceptors has been gradually recognized as an important research field in organic synthesis.^[1] In 2004, Bode and co-workers^[2] and Glorius and Burstein^[3] independently disclosed the first catalytic generation of homoenolate intermediates from enals by using an NHC as a nucleophilic organocatalyst. Later, several extensions have been made with various types of reactive electrophiles to prepare synthetically valuable cyclic as well as acyclic molecular scaffolds via a homoenolate intermediate.^[4] Amongst Michael acceptors, the nitroalkene is probably the most useful electrophile because transformation of the unique nitro group in the resulting product can facilitate further structural elaboration.^[5] Intermolecular organocatalytic C–C bond forming reactions of nitroalkenes can be categorized as follows: (i) the Stetter reaction for the synthesis of β -nitroketones (3-carbon synthons), (ii) Michael reactions involving enolizable aldehydes or ketones for the generation of γ -nitroketones (4-carbon synthons), and (iii) the reaction involving enals to make δ -nitroesters (5-carbon synthons), a reaction that involves an NHC-mediated formation of a homoenolate intermediate (Figure 1).

Scheidt and co-workers first utilized the reaction of a preformed protected thiozolinium carbinol with a nitroalkene, which functioned as a Michael acceptor; the reaction was promoted by a chiral thiourea and fluoride anion and gave β -nitroketone products with moderate *ee* values.^[6] Recently, the research group of Rovis reported an efficient and elegant intermolecular asymmetric Stetter reaction of nitroalkenes; the reaction employed a special type of chiral triazolium-based N-heterocyclic carbene, which contained a fluorine atom in the backbone.^[7] The above methods gave enantiomerically enriched 3-carbon-synthon β -nitroketones. The synthesis of chiral 4-carbon-synthon γ -nitroketones, was also

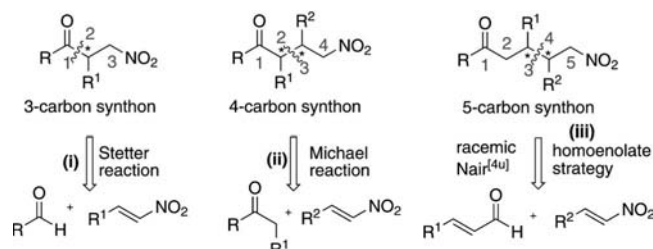


Figure 1. Strategy for a C–C bond formation reaction using nitroalkenes.

extensively investigated by using asymmetric Michael reactions of enolizable carbonyl compounds with nitroalkenes.^[8] The synthesis of γ -nitroketesters and γ -nitroketamides has also been achieved by the activation of 1,2-ketoester and 1,2-ketoanilide pronucleophiles, respectively, for reaction with nitroalkenes.^[9] In 2009, Nair et al. first reported the use of imidazolium-based carbenes for catalyzing the addition of α,β -unsaturated aromatic aldehydes to β -nitrostyrenes, via homoenolate intermediates, to give racemic 5-carbon-synthon nitroester; however, limitations in substrate scope was apparent.^[4a] For the past few years, our research group has engaged in the development of NHC-catalyzed variants of important organic transformations.^[10] We envisaged that a chiral-NHC-catalyzed reaction of enals with a variety of nitroalkenes such as nitrodienes, nitroenynes, and β -nitrostyrenes would give enantiomerically enriched highly functionalized 5-carbon-synthon nitroesters (Figure 1). Notably, these chiral fragments are useful for molecular-scaffold diversification owing to the presence of either an alkene or an alkyne moiety together with a nitro group.^[11] To the best of our knowledge, no suitable direct method for preparing enantiomerically enriched highly functionalized 5-carbon-synthon δ -nitroesters from simple α,β -unsaturated aldehydes has been reported.

We began our investigation on the homoenolate-addition reaction of cinnamaldehyde **1a** with nitrodienene **2a**, as catalyzed by chiral imidazolium carbene precursors **3a–3d**. Whereas the use of imidazolium based chiral precatalysts **3a–3c** gave no reaction, precatalyst **3d** gave the product **4a** in 36% yield, the *syn* diastereoisomer having an *ee* value of 19% (Table 1, entries 1–4).^[12] The use of the triazolium-based precatalyst **3e** and KHCO_3 as a base gave a low yield of **4a** and poor diastereoselectivity (d.r. = 1.4:1) in favor of the *anti* stereoisomer (Table 1, entry 5). The use of mesityl-substituted triazolium precatalyst **3f** in THF gave the

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Table 1: Optimization of the reaction.^[a]

Entry	Precatalyst, Solvent, Base	d.r. [anti/syn] ^[b]	Yield [%] ^[c]	ee [%] ^[d]	
1 ^[e]	3a–3c , THF, K ₂ CO ₃	—	n.r.	—	
2 ^[e]	3a–3d , THF, DBU	—	n.r.	—	
3 ^[e]	3d , THF, K ₂ CO ₃	1:4	24	n.d.	
4 ^[e]	3d , THF, KHCO ₃	1:4	36	19 ^[f]	
5	3e , THF, KHCO ₃	1.4:1	23	n.d.	
6	3f , THF, KHCO ₃	1.7:1	65	86	
7	3f , toluene, KHCO ₃	5.5:1	81	94	
8	3f , xylene, KHCO ₃	5.5:1	67	91	
9	3f , mesitylene, KHCO ₃	6:1	58	95	
10	3f , C ₆ H ₅ CF ₃ , KHCO ₃	4:1	59	86	
11	3f , CH ₂ Cl ₂ , KHCO ₃	1.8:1	82	87	
12	3f , toluene, DIPEA	3:1	60	87	
13	3f , toluene, DMAP	3:1	81	87	
14	3f , toluene, NaOAc	5.5:1	69	94	
15	3f , toluene, K ₂ CO ₃	5.5:1	54	94	
16	3f , toluene, Cs ₂ CO ₃	5.5:1	51	93	
17	3g , toluene, KHCO ₃	6:1	82	95	

[a] Reaction conditions: aldehyde **1a** (2.0 equiv), nitrodiene **2a** (1.0 equiv), chiral precatalyst (10 mol%), base (20 mol%), 24 h.
 [b] Diastereomeric ratio determined by ¹H NMR spectroscopy. [c] Combined yield after column chromatography. [d] The ee values (*anti* diastereoisomer only) were determined by HPLC using a chiral column.
 [e] Reaction was carried out at 70 °C. [f] The ee value of major *syn* diastereoisomer. n.d. = not determined, n.r. = no reaction.

desired product in 65% yield, the major product being the *anti* diastereoisomer, which had an ee value of 86% (Table 1, entry 6). After a preliminary screen of solvents and bases, it was found that the use of triazolium salts **3f** and **3g**, which are derived from mesityl- and 2,6-diethyl-substituted indanolamine, respectively, together with toluene/MeOH (20:1) as the solvent and KHCO₃ as the base afforded **4a** in comparable yields and selectivity (Table 1, entries 7 and 17); the diastereoselectivity was acceptable (**3f**: d.r. = 5.5:1; **3g**: d.r. = 6:1) and the enantioselectivity was high (**3f**: 94%; **3g**: 95%).^[13] To improve the diastereoselectivity, the reaction was carried out using the optimized reaction conditions but at a lower temperature (0 °C); unfortunately, the reaction showed no improvement in diastereoselectivity (d.r. = 6:1) and conversion was incomplete even after 24 h. Therefore, we decided to use chiral carbene precursor **3g** for determining substrate scope (Table 2). Notably, not even a trace amount of Stetter product was observed during the entire optimization

Table 2: Scope of the reaction of nitrodiene.^[a]

Entry	R ¹	R ²	4, Yield [%] ^[b]	d.r. [anti/syn] ^[c]	ee ^[d] [%]
1	Ph	Ph	4a , 82	6:1	95
2	4-MeC ₆ H ₄	Ph	4b , 81	9:1	94
3 ^[e]	4-FC ₆ H ₄	Ph	4c , 81	10:1	99
4 ^[e]	4-MeC ₆ H ₄	4-ClC ₆ H ₄	4d , 68	7:1	92
5 ^[e]	4-BrC ₆ H ₄	2-furyl	4e , 72	10:1	97
6 ^[f]	H	Ph	4f , 48	—	82
7 ^[f]	CH ₃	Ph	4g , 52	5:1	96
8	2-furyl	CH ₃	4h , 86	6:1	97

[a] Reactions performed with 2.0 equiv of **1** and 1.0 equiv of **2** for 24 h.
 [b] Combined yield after column chromatography. [c] Diastereomeric ratio determined from the ¹H NMR spectrum of the crude reaction mixture. [d] The ee values (*anti* diastereoisomer only) were determined by HPLC analysis using a chiral column. [e] *Anti* diastereoisomer isolated in pure form by column chromatography. [f] 3.0 equiv aldehyde added in two portions over a reaction period of 48 h.

study, as concluded by analyzing the ¹H NMR spectra of the crude reaction mixtures.

The scope of this catalytic transformation was determined using a variety of α,β-unsaturated aldehydes using precatalyst **3g**. The reactions of aromatic, aliphatic, and heteroaromatic nitrodiene gave good yields of product, had remarkable levels of enantioselectivity, and had fair to good levels of diastereoselectivity (Table 2). Both electron-rich and electron-deficient α,β-unsaturated aromatic aldehydes are good substrates for this reaction, the corresponding products being isolated with high ee values and in good yields (Table 2; entries 2–5). Even aliphatic α,β-unsaturated aldehydes including the simple nonsubstituted α,β-unsaturated aldehyde, acrolein, gave the desired products in moderate yields with good levels of enantioselectivity (Table 2; entries 6 and 7). An unsaturated aldehydes containing a furyl group also participated in the reaction with aliphatic nitrodiene to give the desired product **4h** in good yield and with high ee value (Table 2; entry 8). The salient feature of this methodology is that the reaction provides exclusively the *anti* diastereomer of the 1,4-Michael addition product; not even a trace amount of 1,6-Michael addition product was observed in the given examples (Table 2). Having established a homoenolate-addition reaction of nitrodiene, we then decided to investigate, using the same optimized reaction conditions, the transformation of nitroenynes, (Table 3). All types of enals, including aromatic as well as heteroaromatic enals, underwent this catalytic transformation smoothly, with good to high levels of enantioselectivity (81–97%) and levels of diastereoselectivity as high as 12:1 (Table 3, entries 1–4). Interestingly, the use of acrolein as a substrate led to the desired product in modest yield and with good ee value (Table 3, entry 5). Finally, we tested this catalytic method using the optimized reaction conditions for the transformation of β-nitrostyrene

Table 3: Scope of the reaction of nitroynes.^[a]

Entry	R ¹	R ²	6 , Yield [%] ^[b]	d.r. [<i>anti:syn</i>] ^[c]	<i>ee</i> [%] ^[d]
1 ^[e]	Ph	Ph	6a , 70	12:1	94
2	4-MeC ₆ H ₄	4-BrC ₆ H ₄	6b , 67	10:1	81
3	2-MeOC ₆ H ₄	4-MeOC ₆ H ₄	6c , 68	9:1	81
4	2-furyl	4-MeOC ₆ H ₄	6d , 78	10:1	97
5 ^[f]	H	4-MeOC ₆ H ₄	6e , 51	—	83

[a] Reactions performed with 2.0 equiv of **1** and 1.0 equiv of **5** for 24–48 h. [b] Combined yield after column chromatography. [c] The d.r. was determined from the ¹H NMR spectrum of the crude reaction mixture. [d] The *ee* values (*anti* diastereoisomer only) were determined by HPLC using a chiral column. [e] Reaction time 48 h. [f] 3.0 equiv of acrolein added in two portions over a reaction period of 48 h.

derivatives. Various enals gave rise to highly functionalized nitroester products **8** and diastereoselectivity in favor of the *anti* product (Table 4). Electron-rich and electron-deficient enals are well tolerated in the reactions with *ortho*- and *para*-substituted nitrostyrene derivatives and give the corresponding products in good yields with high levels of enantioselectivity (95–99%), an exception being *para*-nitro-cinnamaldehyde, the reaction of which had moderate enantioselectivity (81%). The reaction of acrolein with *para*- and *meta*-substituted β -nitrostyrenes gave the desired Michael-addition products with good selectivity (81 and 86% *ee*; Table 4,

Table 4: Substrate scope of reaction of β -nitrostyrenes.^[a]

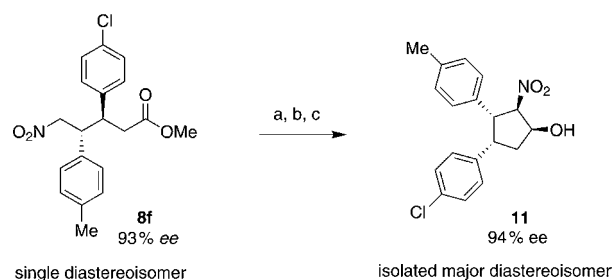
Entry	R ¹	R ²	8 , Yield [%] ^[b]	d.r. [<i>anti:syn</i>] ^[c]	<i>ee</i> [%] ^[d]
1 ^[e]	Ph	Ph	8a , 66	5:1	99
2 ^[f]	4-MeOC ₆ H ₄	4-ClC ₆ H ₄	8b , 58	6:1	91
3	4-MeOC ₆ H ₄	Ph	8c , 78	4.5:1	95
4 ^[f]	4- <i>t</i> BuC ₆ H ₄	4-MeC ₆ H ₄	8d , 63	5:1	97
5	4-ClC ₆ H ₄	2-MeOC ₆ H ₄	8e , 73	10:1	95
6 ^[f]	4-ClC ₆ H ₄	4-MeC ₆ H ₄	8f , 62	10:1	93
7 ^[f]	4-NO ₂ C ₆ H ₄	Ph	8g , 61	9:1	81
8 ^[g]	H	4-MeC ₆ H ₄	8h , 52	—	81
9 ^[g]	H	3-MeOC ₆ H ₄	8i , 51	—	86
10	Ph	cyclohexyl	n.r.	—	—

[a] Reactions performed with 2.0 equiv of **1** and 1.0 equiv of **7** for 24 h. [b] Combined yield after column chromatography. [c] Diastereomeric ratio determined from the ¹H NMR spectrum of the crude reaction mixture. [d] The *ee* values (*anti* diastereoisomer only) were determined by HPLC using a chiral column. [e] Reaction time 48 h. [f] *Anti* diastereoisomer isolated in pure form by column chromatography. [g] 3.0 equiv of acrolein was added in two portions over a reaction period of 48 h.

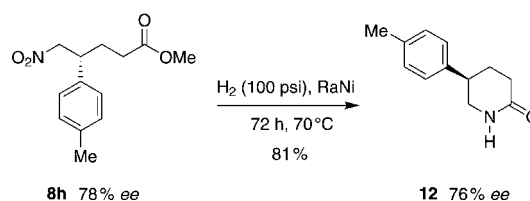
entries 8 and 9, respectively).^[14] Aliphatic nitroalkenes, such as β -cyclohexylnitroalkene, do not participate in this catalytic transformation (Table 4, entry 10).

The relative and absolute stereochemistry of the Michael-addition products **4** and **8** were confirmed by X-ray crystallographic analysis of **4d** and **8b** (see the Supporting Information).^[15] The absolute stereochemistry of Michael-addition product **6** was inferred by analogy.

To establish the importance of this catalytic transformation, we performed a number of reactions with the products of the homoenolate-addition reaction. δ -Nitroester **8f** was reduced to alcohol **9**, which was subsequently oxidized to aldehyde **10**. Next, when treated with a catalytic amount of DABCO, aldehyde **10** underwent smooth conversion into cyclopentanol **11** as a mixture of diastereomers (d.r. = 3:1). The major diastereoisomer of cyclopentanol **11** was isolated in 71% yield (Scheme 1). The homoenolate-addition reaction product **8h** was prepared using the NHC precursor **3f** and was obtained in 51% yield and with an *ee* value of 78%. Compound **8h** was subsequently transformed into δ -lactam **12** in 81% yield and with an *ee* value of 76% when treated with Raney nickel under an atmosphere of hydrogen (Scheme 2).^[16]



Scheme 1. Reaction conditions: a) DIBAL-H (2.2 equiv), toluene, (**9**, 72%); b) DMP (1.2 equiv), CH₂Cl₂, (**10**, 82%); c) DABCO (0.1 equiv), CH₂Cl₂, 48 h, 0 °C, (**11**, 71%). DABCO = 1,4-diazabicyclo[2.2.2]octane, DIBAL-H = diisobutylaluminum hydride, DMP = Dess–Martin periodinane.



Scheme 2. Transformation of a δ -nitroester into a δ -lactam. RaNi = Raney nickel.

In conclusion, we have developed methodology employing catalytic amounts of chiral N-heterocyclic carbene precursors for the synthesis of highly enantiomerically enriched and highly functionalized 5-carbon-synthon δ -nitroesters. A broad range of enals in conjunction with a variety of nitroalkenes, such as nitroalkenes, nitroalkynes, and nitrostyrenes, could be transformed under mild reaction conditions into chiral nitroester compounds with good to high *ee* values.

The products derived from the homoenolate-addition reaction can be easily transformed into highly functionalized enantiomerically enriched cyclopentanol and δ -lactams.

Experimental Section

2,6-Diethyl-substituted triazolium salt **3g** (7.4 mg, 0.017 mmol, 0.1 equiv), KHCO_3 (3.5 mg, 0.034 mmol, 0.2 equiv), and nitrodiene **2a** (30 mg, 0.17 mmol, 1.0 equiv) were added to a 10-mL flask fitted with N_2 balloon. Next, cinnamaldehyde **1a** (45 mg, 0.34 mmol, 2.0 equiv), as a solution in toluene (0.8 mL), and MeOH (40 μL) were added to the reaction mixture. After 24 h, the reaction mixture was diluted with 2–3 mL ethyl acetate and the resulting solution was purified by column chromatography over silica gel using EtOAc/*n*-hexane 1:4 as eluent to afford product **4a** in 82% yield.

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