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Chiral Amino Alcohol-Mediated Asymmetric Conjugate Addition of Arylalkynes to Nitroolefins

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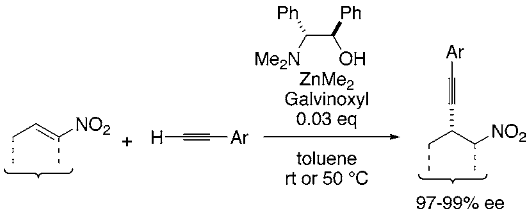
ABSTRACT



The asymmetric reaction of nitroolefins with arylalkynes was mediated by dimethylzinc (or diethylzinc) and (1*R*,2*R*)-2-(dimethylamino)-1,2-diphenylethanol in toluene to provide the corresponding conjugate alkynylation products with high enantiomeric excess of up to 99% in good yields. The presence of 0.03 equiv of galvinoxyl improved the reaction yield.

The asymmetric addition of alkynes to an electron-deficient double bond has been the recent focus of asymmetric reactions.[1] Aldehydes,[2−5] ketones,[6−8] and imines[9−12] are electrophiles that have been well documented by many groups. On the other hand, α,*β*-unsaturated carbonyl compounds or their congeners are acceptors that have seldom accomplished high enantioselectivity.[13−15] The catalytic asymmetric conjugate alkynylation of enones recently re-

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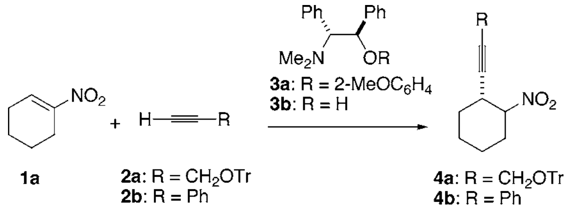
ported by Corey and Chong is the exception.[16] We describe herein that arylalkynes undergo conjugate addition reaction with nitroolefins to provide the corresponding alkynylation adducts with high enantioselectivities of up to 99% ee.

Our approach began with the application of the chiral ligand-controlled asymmetric conjugate addition reaction of aryllithiums with nitroolefins.[17,18] The reaction of lithiated trityl ether of propargyl alcohol **2a** with nitroolefin **1a** in the presence of a tridentate chiral amino ether ligand **3a** in toluene, however, gave the addition product **4a** with a marginal ee of 7% in 96% yield. Reaction of heteroaggregated lithium acetylide of **2a** with a chiral amino alcohol **3b**, the starting material for the preparation of **3a**,[17b] was not successful, giving **4a** with 4% ee in 92% yield.

Table 1. Amino Alcohol **3b**-Mediated Asymmetric Conjugate Addition of **2b** to **1a** Giving **4b**



entry	**2b** (equiv)	**3b** (equiv)	Me_2Zn (equiv)	temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	1.5	1.5	1.5	50	24	39	95
2[c]	1.5	1.5	1.5	rt	120	52	96
3	3	3	3	50	10	66	95
4[d]	3	3	3	rt	30	83	97
5[d,e]	3	3	3	rt	30	74	97
6	3	0	3	50	15	<5	

[a] Combined yield. [b] Ee (%) of *trans*-**4b**. [c] DMPEG (0.1 equiv) was used. [d] Galvinoxyl (0.03 equiv) was used. [e] Diethylzinc was used in place of dimethylzinc.

Promising results were obtained by changing the metal from lithium to zinc (Table 1). The reaction of 1.5 equiv of phenylacetylene **2b** with nitroolefin **1a** was conducted in the presence of 1.5 equiv of **3b** and 1.5 equiv of dimethylzinc in toluene at 50 °C for 24 h to give a 64:36 mixture of *trans*- and *cis*-**4b** with 95% ee and 94% ee, respectively, in 39% yield (Table 1, entry 1). The enantiomeric excess was determined by chiral stationary phase HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 100/1; See Supporting Information). The yield was slightly improved by the addition of 0.1 equiv of poly(ethylene glycol) dimethyl ether (DMPEG)[19] at room temperature for 120 h to give **4b** with 96% ee in 52% yield (entry 2). Screening of solvents (DMSO, THF, acetonitrile, CH_2Cl_2) was not fruitful, giving **4b** with 96−97% ee in 19−43% yield.

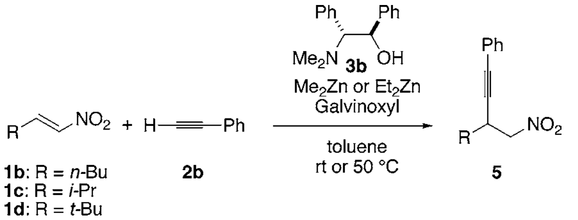
Improvement of the yield was achieved by using 3 equiv each of **2b**, **3b**, and dimethylzinc in toluene at 50 °C for 10 h to give **4b** with 95% ee in 66% yield (entry 3). Much more improvement was obtained upon addition of 0.03 equiv of galvinoxyl to scavenge radicals,[20] giving, after 30 h at room temperature, a 73:27 mixture of *trans*- and *cis*-**4b** with 97 and 96% ee, respectively, in 83% yield (entry 4). Dimethylzinc was replaceable with diethylzinc to give **4b** in comparable enantioselectivity and yield (entry 5). It is also important to note that in the absence of chiral amino alcohol **3b**, the reaction at 50 °C for 15 h gave **4b** in less than 5% yield (entry 6).

It is important to note that saturated ammonium chloride quench of the reaction gave a trans major 73:27 mixture of **4b**, while acetic acid quench favored *cis*-**4b** in a ratio of 81:19. Isomerization of pure *cis*-**4b** of 94% ee was possible by treatment with triethylamine in acetonitrile at room temperature for 24 h to give **4b** as a trans major 71:29 mixture in 95% yield without any racemization.

The chirality controller of amino alcohol **3b** is recoverable in 95% yield by collecting its crystalline hydrochloride after 10% hydrochloric acid treatment of the quenched reaction mixture and is reusable in the asymmetric reaction.

Linear nitroolefins **1b**−**d** (R = *n*-Bu, *i*-Pr, *t*-Bu) were also reacted with phenylacetylene **2b** under the established conditions as above to give the corresponding conjugate alkynylation products **5b**−**d** with 98, 96, and 98% ee, respectively, in moderate to good yields (Table 2). The moderate yields in entries 1 and 2 are due to concomitant deprotonation and isomerization of double bond of **1b** and **1c**.

Table 2. Amino Alcohol **3b**-Mediated Asymmetric Conjugate Addition of **2b** to Linear Olefins **1b**−**d** Giving **5**



entry	**1**	R	temp (°C)	time (h)	yield (%)	ee (%)
1[a]	**1b**	*n*-Bu	rt	24	32	98
2	**1c**	*i*-Pr	rt	72	44	96
3	**1d**	*t*-Bu	50	48	88	98

[a] Diethylzinc was used in place of dimethylzinc.

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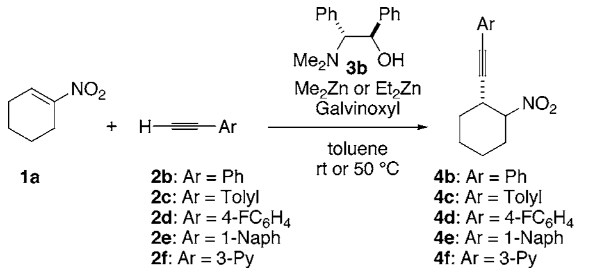
Arylacetylenes are the choice of nucleophiles in the present asymmetric conjugate addition reaction. The reaction of 4-tolyl-, 4-fluorophenyl, 1-naphthyl-, and 3-pyridylacetylenes **2c**−**f** reacted with nitroolefin **1a** to give **4c**−**f** with 96−99% ee in good to moderate yields (Table 3).

Table 3. Amino Alcohol **3b**-Mediated Asymmetric Conjugate Addition of **2b**−**f** to **1a** Giving **4b**−**f**

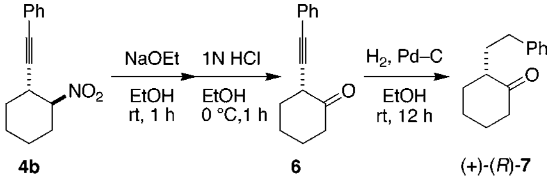


entry	2	Ar	temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	**2b**	Ph	rt	30	83	97
2	**2c**	Tolyl	rt	24	85	98[c]
3	**2d**	$4\text{-}FC_6H_5$	50	20	73	98
4	**2e**	1-Naph	rt	48	82	99
5	**2f**	3-Py	50	48	30	97

[a] Combined yield. The ratio of trans:cis ranges from 73:27 to 21:79 (See Supporting Information). [b] Ee (%) of *trans*-**4** unless otherwise mentioned. [c] Ee (%) of *cis*-**4c**.

The absolute configuration of **4b** was determined to be (*R*)- by the conversion to (+)-**7** with the established absolute configuration (Scheme 1).[21] The absolute configuration of other alkynylation products was tentatively assigned as shown by the reaction analogy.

Scheme 1. Determination of the Absolute Configuration of **4b** by Conversion to the Ketone **7** with the Established Absolute Configuration



The sense of asymmetric induction is predictable by the model **8** originally proposed by Noyori and Oguni[22] in the chiral amino alcohol-mediated catalytic asymmetric alkylation of aldehydes with dialkylzinc reagents (Figure 1). A zinc metal in the bimetallic complex **8** serves as a Lewis acid that coordinates to the oxygen of a nitro group, and then an alkynyl group attacks the double bond to complete the reaction, giving (*R*)-**4b**. The (*R*)-aboslute configuration predicted in **8** is identical with that observed.

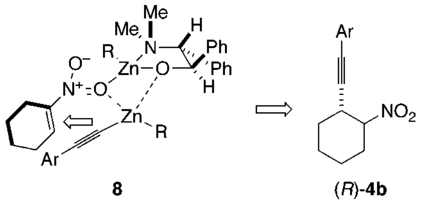
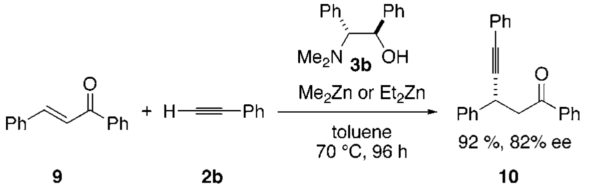


Figure 1. Model **8** predicting the sense of asymmetric induction.

Not only nitroolefin **1** but also enone is the substrate of the asymmetric conjugate alkynylation. The reaction of **2b** with chalcone **9** proceeded smoothly at 70 °C for 96 h to give the conjugate alkynylation product **10**[16a] with 82% ee in 92% yield (Scheme 2). Thus the present conditions have the possibility of being widely applicable to other types of activated olefins.

Scheme 2. Alkynylation of **9** with **2b**



In conclusion, we have developed the highly enantioselective conjugate addition reaction of arylalkyne with nitroolefin by the mediation of chiral amino alcohol and diorganozinc. However, development of a catalytic protocol and the use of a nonarylalkyne are the targets of the next stage.

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Supporting Information Available: Reaction procedure and the characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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