

Direct Asymmetric Michael Addition to Nitroalkenes: Vinylogous Nucleophilicity under Dinuclear Zinc Catalysis

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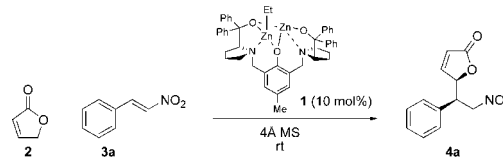
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The Michael addition is certainly one of the most powerful bond-forming transformations, and the diversity in donors and acceptors that can be combined is remarkable. Recent efforts have focused on the development of efficient methods to perform direct, asymmetric Michael addition reactions, and notable success has been achieved by using both organocatalysis¹ and transition metal catalysis.² The self-assembled dinuclear complexes generated from our Bis-ProPhenol ligand and adequate metal sources³ are potentially suitable catalysts.⁴ The complementary reactivity of the two metal centers allows for dual activation whereas conformational rigidity enables chiral recognition, as illustrated in a variety of direct asymmetric addition reactions and desymmetrization processes.⁵ Selecting the Michael addition to nitroalkenes as a probe reaction, we decided to incorporate a new concept into our general strategy, namely vinylogous nucleophilicity.^{6,7} As the donor, 2(5*H*)-furanone **2** was envisioned to be a challenging yet ideal candidate to demonstrate the synthetic efficiency of our system. Indeed, this commonly utilized nucleophile usually requires preactivation as a siloxydiene à la Mukaiyama,⁸ and direct approaches are consequently highly valuable from the standpoint of atom economy. While such a strategy was reported in a stereoselective vinylogous 1,2-addition,⁹ the direct use of **2** in asymmetric conjugate addition has not been precedented.

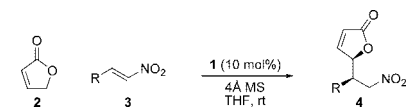
As previously reported,³ the dinuclear zinc complex **1** was prepared by treating the commercially available (*S,S*)-Bis-ProPhenol ligand with 2 equiv of Et₂Zn. Early optimization with Michael acceptor **3a** proved that **1** was competent at promoting the alkylation of butenolide **2** at the γ -position at room temperature. Among the solvents that were screened, THF gave the highest diastereoselectivity (Table 1, entries 1–4). Interestingly, the reaction proceeded faster in toluene with similar yield and enantioselectivity. Dilution had a beneficial effect on the diastereoselectivity: Michael adduct **4a** was obtained with 10:1 dr by lowering the concentration of nitroalkene to 0.25 M (entry 5). Upon dilution to 0.125 M, diastereoselectivity could be further improved to 17:1 dr, albeit at the expense of an extended reaction time (entry 6).

Adopting the conditions described in Table 1, entry 5 as the optimal compromise between reactivity and stereoselectivity, the generality of the method was demonstrated by evaluating a variety of nitroalkenes (Table 2). β -Nitrostyrenes (entries 1–5) tolerated substitution at any position of the aromatic ring, and both electron-donating and electron-withdrawing functionalities were compatible. The electron-rich substrate **3d** gave the best results: the corresponding adduct **4d** was obtained in 78% yield with 20:1 dr and 96% ee (entry 3). In the case of the 1-naphthyl derivative **3g**, excellent diastereo- and enantioselectivity were achieved as well (entry 6). Nitroalkenes bearing heteroaromatic β -Substituents were also suitable substrates as exemplified by the preparation of both regioisomers **4h** and **4i** in 95% ee (entries 7 and 8). Similarly good yields and stereoselectivities were observed with the thiophene counterparts (entries 9 and 10). The indole-substituted nitroalkene

Table 1. Selected Optimization Results^a

entry	solvent	[nitroalkene]	time (h)	yield (%) ^b	dr ^c	ee (%) ^d
1	THF	0.5 M	19	75	8:1	91
2	toluene	0.5 M	8	71	5:1	92
3	Et ₂ O	0.5 M	26	40	1:1	65
4	dioxane	0.5 M	22	69	6:1	93
5	THF	0.25 M	19	76	10:1	91
6	THF	0.125 M	35	71	17:1	92

^a All reactions were carried out using 1 equiv of **3a** (0.50 mmol), 2 equiv of **2**, 0.10 equiv of (*S,S*)-complex **1**, and 100 mg of 4 Å MS. ^b Refers to the isolated mixture of diastereoisomers. ^c Determined by ¹H NMR of the crude reaction mixture. ^d Enantiomeric excess of the major diastereoisomer, determined by chiral HPLC.

Table 2. Variation of the Nitroalkene^a

entry	R	product	yield (%) ^b	dr ^c	ee (%) ^d
1	2-Me-Ph (3b)	4b	74	8:1	92
2	4-Me-Ph (3c)	4c	70	17:1	95
3	4-MeO-Ph (3d)	4d	78	20:1	96
4	4-Cl-Ph (3e)	4e	70	9:1	90
5	3-Br-Ph (3f)	4f	72	7:1	87
6	1-naphthyl (3g)	4g	75	>20:1	94
7	2-furanyl (3h)	4h	77	18:1	95
8	3-furanyl (3i)	4i	65	14:1	95
9	2-thiophenyl (3j)	4j	69	>20:1	94
10	3-thiophenyl (3k)	4k	71	17:1	95
11 ^{e,f}	<i>N</i> -Boc-3-indolyl (3l)	4l	73	6:1	85
12 ^e	PhCH ₂ CH ₂ (3m)	4m	47	4:1 ^g	83
13 ^e	PhCHCH (3n)	4n	52	3:1	91

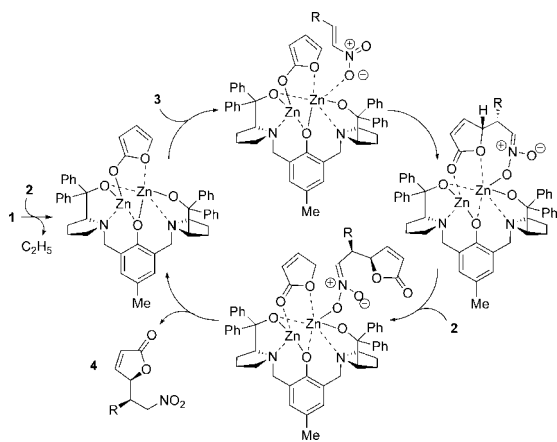
^a All reactions were carried out using 1 equiv of nitroalkene **3** (0.50 mmol, 0.25 M), 2 equiv of **2**, 0.10 equiv of (*S,S*)-complex **1**, and 100 mg of 4 Å MS. ^b Refers to the isolated mixture of diastereoisomers. ^c Determined by ¹H NMR of the crude reaction mixture. ^d Enantiomeric excess of the major diastereoisomer, determined by chiral HPLC. ^e Reaction performed in toluene instead of THF. ^f Results using THF: 60% yield, 7:1 dr, 62% ee. ^g Determined by chiral HPLC.

3l proved to be a more challenging acceptor under the optimized conditions. However, switching the solvent to toluene improved the yield and the enantioselectivity (entry 11). As it could be expected from the optimization studies, toluene was also more appropriate for the less reactive aliphatic substrate **3m** and the corresponding Michael adduct was isolated in 47% yield with 4:1 dr and 83% ee (entry 12). Similarly, starting from the 1-nitro-1,3-

diene **3n** the 1,4-addition product **4n** was obtained with moderate yield and diastereoselectivity but with high enantioselectivity (entry 13). In several instances, the stereoisomeric purity of the Michael adducts could be enhanced by recrystallization. For example, product **4a** could be isolated with 20:1 dr and 98% ee with excellent mass recovery (65% yield from **3a**). Moreover, crystals from chloride **4e** were suitable for an X-ray analysis which established the *syn* stereochemical outcome of the reaction as well as the absolute configuration. The stereochemistry of the other Michael adducts **4** was assigned by analogy.

A tentative catalytic cycle that accounts for the observed stereoselectivity is depicted in Scheme 1. Binding of the nucleophile as a bidentate bridging aromatic enolate^{3b,10} would ensure diastereoselection in the attack on the electrophile activated by complexation to the Lewis acidic zinc atom in the indicated orientation. Formation of the new C–C bond within this highly organized environment would lead to a zinc nitronate intermediate. Finally, proton transfer with an incoming molecule of nucleophile would release product **4** and complete the catalytic cycle. The fact that open coordination sites remain on the zinc that may allow additional entities present to ligate and thereby modify the nature of the chiral space may account for the dilution effect.^{3d}

Scheme 1. Proposed Catalytic Cycle

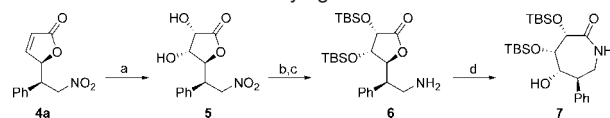


The Michael adducts **4** are versatile building blocks as one can envision further elaboration of both the butenolide moiety and the nitro functionality. Compound **4a** served as a model to straightforwardly illustrate this synthetic potential (Scheme 2). Thus, Ru-catalyzed *cis*-dihydroxylation¹¹ of the conjugated olefin led to diol **5** in 76% yield with complete diastereoselectivity.¹² In this way, excellent control was achieved over four adjacent stereocenters, newly created in only two steps from **3a**. The hydroxyl groups were masked as silyl ethers to avoid handling of otherwise highly polar products resulting from the reduction of the nitro substituent. The latter transformation proceeded smoothly under standard conditions to afford the densely functionalized primary amine **6**. Spontaneously, upon standing neat at rt the isolated amine slowly evolved into lactam **7**. Interestingly, similar polyhydroxyazepanones are being actively investigated in search of potent glycosidase inhibitors.¹³

In summary, synthetically versatile γ -substituted butenolides were prepared stereoselectively by direct asymmetric Michael addition to nitroalkenes.¹⁴ This extension of the scope of our dinuclear zinc catalyst showcases its ability to promote vinylogous nucleophilicity.

We believe this reactivity feature paves the way for a wide diversity of potential donors, and further exploration is currently underway.

Scheme 2. Elaboration of a Vinylogous Michael Adduct^a



^a Conditions: (a) RuCl₃·6H₂O (7 mol%), NaIO₄ (1.5 equiv), CH₃CN/H₂O 5:1, 0 °C, 76% yield; (b) TBSOTf (3 equiv), 2,6-lutidine (3 equiv), CH₂Cl₂, 0 °C to rt, 84% yield; (c) 10% Pd/C, 1 atm of H₂, MeOH, rt, 69% yield; (d) neat, rt, 7 d.

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Supporting Information Available: Detailed experimental procedures and characterization data for **4**–**7**; CIF file for **4e** and **5**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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