Ni(II)–Bis[(R , R)- N , N ‘-dibenzylcyclohexane-1,2-diamine]Br 2 Catalyzed Enantioselective Michael Additions of 1,3-Dicarbonyl Compounds to Conjugated Nitroalkenes

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Ni(II)−Bis[(*R*,*R*)-*N*,*N*′-dibenzylcyclohexane-1,2-diamine]Br_2 Catalyzed Enantioselective Michael Additions of 1,3-Dicarbonyl Compounds to Conjugated Nitroalkenes

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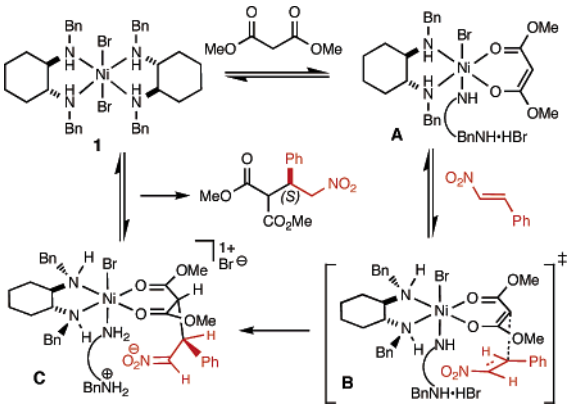
The continued interest in the development of direct catalytic addition processes such as the Michael reaction is based on the wide variety of synthetically useful chiral building blocks that are readily assembled in the event that such processes can be rendered enantioselective.[1] Products resulting from the enantioselective addition of nucleophiles to conjugated nitroalkenes[2,3] represent attractive targets largely due to the attributes of the nitro group associated with its range of subsequent transformations.[4] Recent studies by others have led to the development of catalytic enantioselective additions of 1,3-dicarbonyl compounds to conjugated nitroalkenes.[5] The purpose of this communication is to introduce a new, readily prepared, chiral Ni(II) catalyst **1** that facilitates this enantioselective transformation at ambient temperatures (Scheme 1).

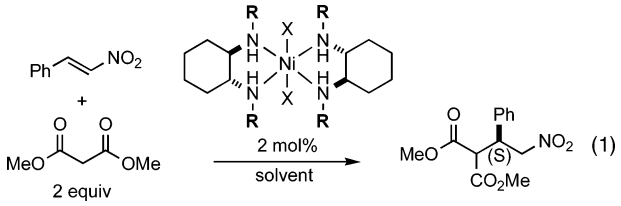
Scheme 1



Catalyst design was based on the hypothetical catalytic cycle illustrated in Scheme 1. To effect the prerequisite 1,3-dicarbonyl enolizations, we envisioned the use of a catalyst such as **1**, consisting of a moderately Lewis acidic metal salt bound to two (neutral) chiral ligands. The latter should be basic enough to effect substrate enolization, alleviating the need for the addition of ancillary base.[6] After substrate enolization, one diamine ligand is partially released as its conjugate acid, resulting in formation of the enolate **A**. Nucleophilic attack of **A** on nitrostyrene could proceed through plausible transition structure **B**, where reinforcing steric and electrostatic effects might orient the nitrostyrene moiety. Intramolecular proton transfer from the pendant ammonium ion to the nitronate anion in **C** and subsequent product dissociation complete the catalytic cycle.

Following considerable experimentation, readily accessible nickel complexes, such as the bench-stable compound **1**, emerged as useful catalysts.[6−9] Table 1 shows the effect of catalyst structure and solvent on the reaction time and selectivity. While the nickel complex derived from unsubstituted cyclohexanediamine proved to be a very poor catalyst (Table 1, entry 1), complexes derived from substituted versions of this ligand readily catalyzed the desired transformation. While the dibenzyl substituted cyclohexanediamine exhibited the best performance among the ligands tested, complex **1** also showed the best solubility through a range of solvents.

Table 1. Catalyst Survey for the Michael Addition of Dimethyl Malonate to Nitrostyrene (eq 1)[a]



entry	R	X	solvent	time (h)	ee (%)[b]
1	H	Br	EtOH/PhMe	ND[c]	6
2	−CH_2(α-naphth)	Br	THF	ND	93
2	−CH_2(2,6-Cl_2Ph)	Br	CH_2Cl_2/PhMe	13	90
4	Bn	Br	THF	10	94
5	Bn	Br	EtOAc	10	94
6	Bn	Br	CH_2Cl_2	7	92
7	Bn	Br	EtOH	24	81
8	Bn	Br	PhMe	8	95
9	Bn	Cl	PhMe	10	94
10	Bn	I	PhMe	10	94
11	Bn	OAc	PhMe	>52	91
12	Bn	OTf	PhMe	24	92
13	Bn	SbF_6	PhMe	>48	86

[a] All reactions were performed at room temperature on a 0.25 mmol scale and at a 0.25 M concentration. Reactions were run at room temperature to 100% conversion. [b] Enantiomeric excess was determined by HPLC using a Chiracel AD column. [c] Reaction is very sluggish; low conversion after 8 days.

Interestingly, while a number of different counteranions are tolerated, the use of $NiBr_2$ afforded the best results for reactions conducted in toluene (Table 1, entry 8).[10] Further optimization of reaction conditions showed little change in rate and selectivity when the amount of malonate was reduced to 1.2 equiv while increasing the concentration to 1 M. The scope of the malonate addition under optimized reaction conditions is summarized in Table 2. Uniformly high yields and enantioselectivities are obtained for a broad range of substituted and unsubstituted malonates (Table 2, entries 1−7). Variation of the aromatic residue on the nitroalkene was also well tolerated (entries 8−15) in the reaction with diethyl malonate. While the reactivities of alkyl substituted nitroalkenes are diminished (entries 16−18), reasonable reaction rates may be achieved upon performing the reactions under neat conditions, giving rise to product with slightly lower enantiomeric excess.

The scope of this reaction may be extended to the use of β-ketoester nucleophiles (Table 3). Excellent yields and good selectivities in the β-position to the nitro group were obtained, regardless of the nature of the two substituents on the β-ketoester

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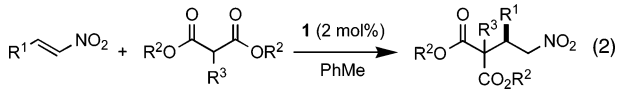
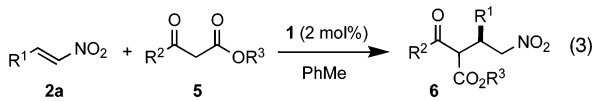
Table 2. Scope of the Malonate Addition to Nitroalkenes (eq 2)[a]



entry	R^1	R^2	R^3	product	time (h)	yield (%)[b]	ee (%)[c]
1	Ph	Me	H	**4a**	4	99	94
2	Ph	Et	H	**4b**	5	99	95
3	Ph	*i*-Pr	H	**4c**	10	96	95
4	Ph	*t*-Bu	H	**4d**	36	97	95
5	Ph	Bn	H	**4e**	6	99	95
6	Ph	Me	Me	**4f**	48	95	95
7	Ph	Et	NHAc	**4g**	72	92	94
8	4-Me−Ph	Et	H	**4h**	7	99	95
9	4-MeO−Ph	Et	H	**4i**	7	99	95
10	4-Br−Ph	Et	H	**4j**	8	99	95
11	2-Cl−Ph	Et	H	**4k**	6	98	92
12	2,3-(MeO)−Ph	Et	H	**4l**	15	99	93
13	2,4-(MeO)−Ph	Et	H	**4m**	72	98	94
14	3,4-OCH_2O−Ph	Et	H	**4n**	36	97	95
15	2-furyl	Et	H	**4o**	14	98	95
16[d]	*n*-C_5H_{11}	Et	H	**4p**	48	84	89
17[d]	$CH_2CH(Me)_2$	Et	H	**4q**	120	94	88
18[d]	$CH(Me)_2$	Et	H	**4r**	96	82	90

[a] All reactions were performed on a 1 mmol scale with 2 mol % of the preformed catalyst **1** at a 1 M concentration using 1.2 equiv of the 1,3-dicarbonyl compound and toluene as the solvent. Reactions were run at room temperature in a screw-capped vial for the indicated time. [b] All yields are isolated yields after chromatographic purification. [c] Enantiomeric excess was determined by HPLC using Chiracel OD-H, OJ-H, AD, or AD-H columns. [d] Conducted neat with 2 equiv of diethyl malonate.

Table 3. Scope of the β-Ketoester Addition to Nitrostyrene (eq 3)[a]



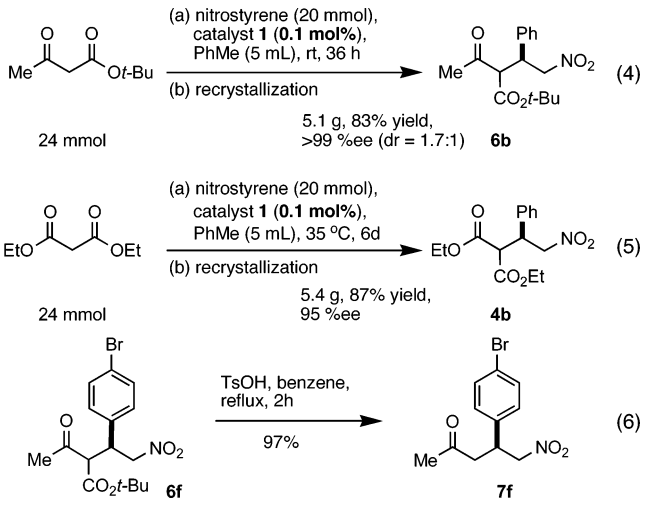
entry	R^1	R^2	R^3	product	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1[e]	Ph	Me	Me	**6a**	6	94	1:1	94 (94)
2	Ph	Me	Et	**6b**	2	96	1:1	93 (93)
3[e]	Ph	Me	*t*-Bu	**6c**	5	97	1.5:1	93 (93)
4	Ph	CH_2Me_2	Et	**6d**	4	96	1:1	93 (93)
5	Ph	Ph	Et	**6e**	4	99	2.5:1	90 (85)
6[e]	4-Br−Ph	Me	*t*-Bu	**6f**	5	97	1.7:1	94 (91)

[a,b] See Table 2. [c] Determined by ^{1}H NMR. [d] Enantioselectivity in β-position to nitro group for major (minor) diastereomer; determined by HPLC using a Chiracel AD-H column. [e] Reaction was performed in THF.

moiety. Generally, these reactions are slightly faster than their malonate counterparts.

The utility of the process was further evaluated by performing large-scale experiments. As highlighted in eqs 4 and 5, *tert*-butyl acetoacetate and diethyl malonate, respectively, may be added to nitrostyrene in a highly effective manner by employing only 0.1 mol % of catalyst. This probably represents the lower limit for the catalyst:substrate ratio due to the extended reaction times. In addition, the products derived from *tert*-butyl acetoacetate can readily be transformed into γ-nitroketones (eq 6).

Transition structure **B** in Scheme 1 provides an attempt to rationalize the observed sense of stereoinduction. Overall dipole reduction and minimization of ligand−substrate interactions could be the dominant factors accounting for the high enantioselectivities. At the present time, we have no information as to the disposition of the monoprotonated ligand. While our illustrations suggest that it may still be coordinated to the Ni-center through the remaining



basic nitrogen atom, we have no evidence for this point. Further studies will be necessary to fully elucidate the mechanism.

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Supporting Information Available: Experimental procedures, spectral data for all compounds, and stereochemical proofs (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) It is interesting to note that the free ligand catalyzes the reaction by itself when run in EtOH, giving rise to racemic product.

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