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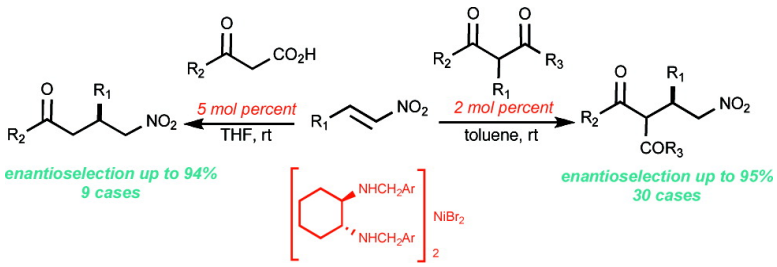

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Scope and Mechanism of Enantioselective Michael Additions of 1,3-Dicarbonyl Compounds to Nitroalkenes Catalyzed by Nickel(II)−Diamine Complexes

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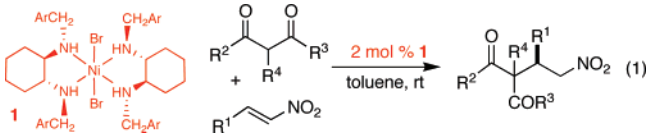
Abstract: Readily prepared Ni(II)-*bis*[(*R*,*R*)-*N*,*N*′-dibenzylcyclohexane-1,2-diamine]Br_2 was shown to catalyze the Michael addition of 1,3-dicarbonyl compounds to nitroalkenes at room temperature in good yields with high enantioselectivities. The two diamine ligands in this system each play a distinct role: one serves as a chiral ligand to provide stereoinduction in the addition step while the other functions as a base for substrate enolization. Ligand modification within the catalyst was also investigated to facilitate the reaction of aliphatic nitroalkenes, 1,3-diketones, and β-ketoacids. Ni(II)-*bis*[(*R*,*R*)-*N*,*N*′-di-*p*-bromo-benzylcyclohexane-1,2-diamine]Br_2 was found to be an effective catalyst in these instances. Furthermore, monodiamine complex, Ni(II)-[(*R*,*R*)-*N*,*N*′-dibenzylcyclohexane-1,2-diamine]Br_2, catalyzed the addition reaction in the presence of water. The proposed model for stereochemical induction is shown to be consistent with X-ray structure analysis.

Introduction

The Michael addition and its variants are versatile carbon−carbon bond constructions,[1] and catalytic enantioselective variants have been under development in recent years.[2] Among the array of activated olefins, nitroalkenes are attractive as the resulting products are useful intermediates by virtue of the range of subsequent transformations that are associated with the nitro group such as the synthesis of chiral γ-amino acids and five-membered nitrogen heterocycles.[3−5] Metal enolates have been employed extensively in the construction of functionalized building blocks and thus stand as the important nucleophilic partner in these addition reactions.[2d,g,6] The purpose of this publication is to describe the scope and mechanistic details of the enantioselective nitroalkene Michael addition of 1,3-dicarbonyl nucleophiles catalyzed by the chiral Ni(II) complex **1** that facilitates this transformation at ambient temperatures (eq 1).



(1)

Background. 1,3-Dicarbonyl compounds are promising enolate candidates for the development of asymmetric Lewis acid-catalyzed reactions because of their ability to engage in two-point binding to a chiral metal complex thus allowing for a chelate-ordered transition state. For this reason, the Michael

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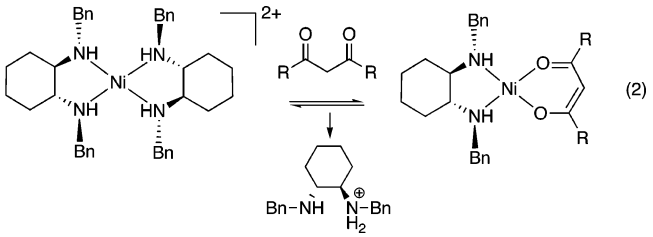
addition of 1,3-dicarbonyl compounds catalyzed by metal−ligand complexes, based on palladium,[7] scandium,[8] copper,[9] aluminum,[10] nickel,[11] magnesium,[12] iridium,[13] ruthenium,[14] lanthanum,[15] and hetero-bimetallic alminium−lithium[16] complexes have been investigated.

Recent studies have led to the rapid development of catalytic enantioselective additions of 1,3-dicarbonyl compounds to nitroalkenes, particularly those reactions subject to organocatalysts.[17] However, the analogous transformation using chiral metal catalysts is still rare,[11g,12,14] and the achievement of high enantioselectivities with low catalyst loading remains an ongoing goal. The first reported example by Barnes and co-workers employed a Mg(II) bis(oxazoline) complex as a chiral catalyst in the presence of an amine cocatalyst (*N*-methylmorpholine).[12a] Dicarbonyl substrate coordination to the Lewis acidic metal−ligand complex increases the acidity of the former thus facilitating its deprotonation by a weak amine cocatalyst to generate the required metal enolate. This technique, come to be known as "soft enolization," has become popular in chiral Lewis acid-catalyzed enantioselective reactions due to the mildness of the enolization conditions.[18]

The chiral catalyst complex in the present study consists of $NiBr_2$ coordinated to two chiral diamine ligands. It was felt that complexation of the bidentate substrate to the metal center might liberate one of the diamine ligands enabling it to function as a base, thus removing the need for the addition of an ancillary base (eq 2). Thus, the ligand would be able to fulfill a dual role: it might function not only as a chiral scaffold, but also one of the liberated diamine ligands might serve as the base for substrate deprotonation.



(2)

The following discussion details the scope of the enantioselective "nitroalkene-Michael" addition reaction (eq 1). The discussion includes, kinetic studies, a probe of nonlinear effects, the characterization of intermediate substrate-catalyst complexes by X-ray crystallography, and the elaboration of the Michael adducts into chiral 5-membered nitrogen heterocycles.

Results and Discussion

Catalyst Design and Activity. During our ongoing efforts to develop new asymmetric Lewis acid-catalyzed transformations,[19] the readily prepared and bench-stable nickel complexes **1** emerged as viable catalysts.[11g,20,21] Table 1 shows the effect of solvent and counterions of the nickel catalyst **1** on the reaction time and selectivity for the Michael addition of dimethyl malonate to nitrostyrene. Interestingly, while a number of different counterions are tolerated (entries 5−10), the use of

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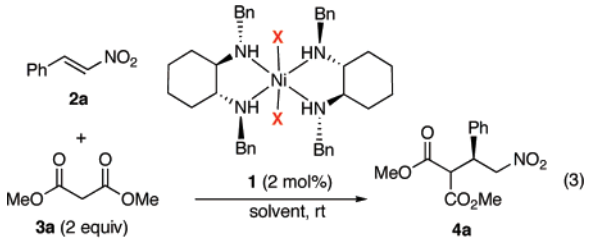
$NiBr_2$, catalyst **1a**, showed good solubility through a range of solvents and afforded the best results for the reaction conducted in toluene (entry 5). The crystal structure of catalyst **1a** shown in Figure 1 reveals that the two diamine ligands coordinate to nickel in a trans geometry while two bromides occupy the apical positions.

The temperature profile for the addition of diethyl malonate to nitrostyrene catalyzed by **1a** was investigated (Figure 2). Remarkably good levels of enantioselectivity were maintained even at elevated reaction temperatures (e.g., 85% ee at 100 °C). For convenience, the reactions for the rest of this study were conducted at room temperature.

Table 1. Counterion and Solvent Survey for the Michael Addition of Dimethyl Malonate to Nitrostyrene[a]



entry	X		solvent	time (h)	ee (%)[b]
1	Br	(**1a**)	THF	10	94
2	Br	(**1a**)	EtOAc	10	94
3	Br	(**1a**)	CH_2Cl_2	7	92
4	Br	(**1a**)	EtOH	24	81
5	Br	(**1a**)	toluene	8	95
6	Cl	(**1b**)	toluene	10	94
7	I	(**1c**)	toluene	10	94
8	OAc	(**1d**)	toluene	>52	91
9	OTf	(**1e**)	toluene	24	92
10	SbF_6	(**1f**)	toluene	>48	86

[a] All reactions were performed at room temp on 0.25 mmol scale at 0.25 M concentration and were allowed to reach 100% conversion. [b] Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel AD column.

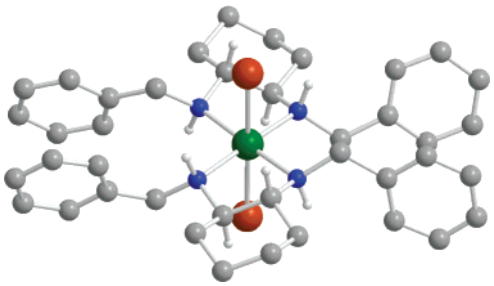


Figure 1. Crystallographic structure of Ni(II)-*bis*[(*R*,*R*)-*N*,*N*′-dibenzylcyclohexane-1,2-diamine]Br_2 (**1a**).

Stereochemical Assignments. In the ensuing discussion, the absolute stereochemical assignment of the 2-substituent is as indicated in the graphics. In all instances, enantiomeric excesses were determined after decarboxylation. Individual stereochemical assignments are discussed in the Supporting Information.

Reaction Scope. The scope of the malonate addition under optimized reaction conditions is summarized in Table 2.[22] The

(22) When the amount of malonate was reduced to 1.2 equiv while increasing the concentration to 1 M in the addition reaction, the reaction rate and selectivity increased.

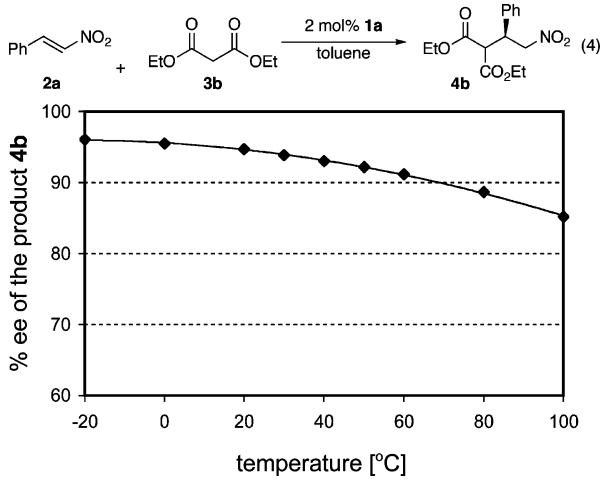
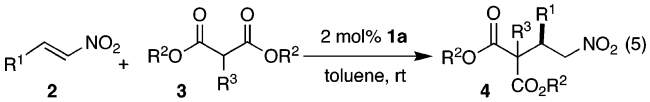


Figure 2. Temperature profile for the addition of diethyl malonate to nitrostyrene catalyzed by **1a**.

Table 2. Scope of the Malonate Michael Addition with Nitroalkenes[a]

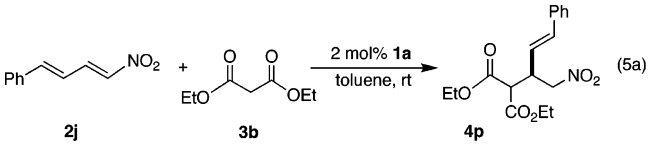


entry	R^1	R^2	R^3	time (h)	yield (%)	ee (%)[b]
1	Ph (**2a**)	Me	H (**3a**)	4	99 (**4a**)	94
2	Ph (**2a**)	Et	H (**3b**)	5	99 (**4b**)	95
3	Ph (**2a**)	*i*-Pr	H (**3c**)	10	96 (**4c**)	95
4	Ph (**2a**)	*t*-Bu	H (**3d**)	36	97 (**4d**)	95
5	Ph (**2a**)	Bn	H (**3e**)	6	99 (**4e**)	95
6	Ph (**2a**)	Me	Me (**3f**)	48	95 (**4f**)	95
7	Ph (**2a**)	Et	NHAc (**3g**)	72	92 (**4g**)	94
8	4-Me−Ph (**2b**)	Et	H (**3b**)	7	99 (**4h**)	95
9	4-MeO−Ph (**2c**)	Et	H (**3b**)	7	99 (**4i**)	95
10	4-Br−Ph (**2d**)	Et	H (**3b**)	8	99 (**4j**)	95
11	2-Cl−Ph (**2e**)	Et	H (**3b**)	6	98 (**4k**)	92
12	2,3-(MeO)-Ph (**2f**)	Et	H (**3b**)	15	99 (**4l**)	93
13	2,4-(MeO)-Ph (**2g**)	Et	H (**3b**)	72	98 (**4m**)	94
14	3,4-OCH_2O−Ph (**2h**)	Et	H (**3b**)	36	97 (**4n**)	95
15	2-furyl (**2i**)	Et	H (**3b**)	14	98 (**4o**)	95
16	*trans*-PhCH=CH (**2j**)	Et	H (**3b**)	30	95 (**4p**)	95
17	$Ph(CH_2)_2$ (**2k**)	Et	H (**3b**)	48	94 (**4q**)	89
18[c]	*n*-C_5H_{11} (**2l**)	Et	H (**3b**)	48	84 (**4r**)	89
19[c]	$(Me)_2CHCH_2$ (**2m**)	Et	H (**3b**)	120	94 (**4s**)	88
20[c]	$(Me)_2CH$ (**2n**)	Et	H (**3b**)	96	82 (**4t**)	90

[a] All reactions were performed on 1 mmol scale with 2 mol % of **1a** at 1 M concentration using 1.2 equiv of the 1,3-dicarbonyl compound. [b] Enantiomeric excess was determined by chiral HPLC analysis using Chiralcel OD−H, OJ-H, AD, or AD-H columns. [c] Conducted neat with 2 equiv of diethyl malonate.

reaction time is dependent on the steric demands of the malonate residue. When the alkyl ester group (R^2) was changed from methyl (**3a**) to *t*-butyl (**3d**) the required reaction time for was increased by 9-fold. Application of substituted malonates **3f** and **3g** ($R^3 \neq H$) had an even more significant effect upon reaction rate. Nevertheless, uniformly excellent yields and enantioselectivities were obtained for a broad range of malonate additions with nitrostyrene **2a** (R^1 = Ph, entries 1−7). Furthermore, the reaction of diethyl malonate **3b** with electron-rich and electron-poor 2-aryl substituted nitroalkenes was equally efficient (entries 8−15). In addition, 1-nitro-4-phenyl butadiene (**2j**) (R^1 = HC=

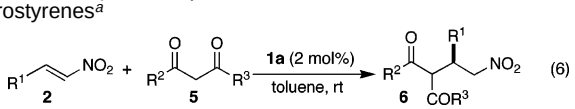
CHPh) was also shown to be a highly efficient activated alkene (entry 16, eq 5a). It is noteworthy that no 1,6-addition was observed.



In contrast to the nitrostyrene derivatives, substrates possessing aliphatic-2-substituents **2k**−**n** exhibited diminished reactivity (entries 17−20). Reasonable reaction rates were only achieved in these cases by performing the reactions neat, and lower enantiomeric excesses resulted (entries 18−20). This deficiency will be addressed in subsequent temperature and ligand optimization studies (vide infra).

The scope of this reaction was also extended to the use of β-ketoesters and 1,3-diketones (Table 3). When β-ketoesters were employed, excellent yields and good enantioselectivities at the position β-to the nitro group were obtained, regardless of the nature of the two substituents on the β-ketoester **5a**−**e** (entries 1−6). 1,3-Diketones **5f** and **5g** are also applicable to the present catalytic system, although the reactions proceeded slower, and both yields and enantioselectivities were diminished (entries 7 and 8).

Table 3. Scope of the β-Ketoester and 1,3-Diketone Additions to Nitrostyrenes[a]

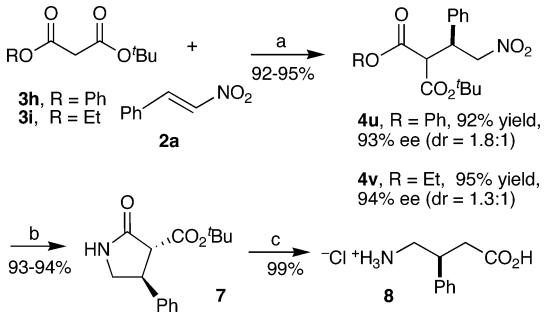


entry	R^1	R^2	R^3	time (h)	yield (%)	dr[b]	ee (%)[c]
1[d]	Ph (**2a**)	Me	OMe (**5a**)	6	94 (**6a**)	1:1	94 (94)
2	Ph (**2a**)	Me	OEt (**5b**)	2	96 (**6b**)	1:1	93 (93)
3[d]	Ph (**2a**)	Me	O^{t}Bu (**5c**)	5	97 (**6c**)	1.5:1	93 (93)
4	Ph (**2a**)	$CHMe_2$	OEt (**5d**)	4	96 (**6d**)	1:1	93 (93)
5	Ph (**2a**)	Ph	OEt (**5e**)	4	99 (**6e**)	2.5:1	90 (85)
6[d]	4-Br−Ph (**2d**)	Me	O^{t}Bu (**5c**)	5	97 (**6f**)	1.7:1	94 (91)
7	Ph (**2a**)	Me	Me (**5f**)	110	84 (**6g**)		86
8	Ph (**2a**)	Et	Et (**5g**)	148	90 (**6h**)		87

[a] All reactions were performed on a 1 mmol scale with 2 mol % of **1a** at 1 M concentration using 1.2 equiv of the 1,3-dicarbonyl compound. [b] Determined by ^{1}H NMR spectroscopy. [c] Enantioselectivity at the β-position for major (minor) diastereomer as determined by chiral HPLC analysis using a Chiralcel AD-H column. [d] Reaction was performed in THF.

Applications. We previously demonstrated that this methodology is amenable to large-scale preparations with good results being achieved even at 0.1 mol % catalyst loading.[11g] The utility of this procedure was next demonstrated in the enantioselective synthesis of β-phenyl-γ-amino butanoic acid (**8**). The parent γ-amino butanoic acid (GABA) is an important target for enantioselective synthesis because it is a principle mammalian neurotransmitter,[23] and its derivatives are commonly found in natural products and pharmaceutical agents. The GABA derivative **8** would be readily accessible from γ-lactam **7** which could be derived from the product of Michael addition of a 1,3-diester to nitrostyrene.

Scheme 1. Synthesis of β-Phenyl-γ-aminobutanoic Acid 8[a]



[a] Reaction conditions: (a) catalyst **1a** (2 mol %), toluene, room temp, 36 h; (b) $NiCl_2 \cdot 6H_2O/NaBH_4$, MeOH, room temp, 7 h; (c) 6 N HCl, reflux, 24 h.

The following route was selected to be optimal in terms of overall yield, stereoselectivity, and simplicity (Scheme 1). The Michael additions of malonate **3h** or **3i** to nitrostyrene furnished **4u** and **4v** in 93% and 95% yield, respectively. Reduction of the nitro moiety in **4u** or **4v** with $NaBH_4$, in the presence of nickel(II) chloride, was followed by spontaneous cyclization with the more reactive esters to afford the thermodynamically more stable trans-γ-lactam **7** as a single diastereomer. The stereoselection for trans-isomer **7** indicates that epimerization of the stereogenic center α-to the carbonyl groups is facile under the reaction conditions. When **7** was heated at reflux in 6 N HCl, hydrolysis of both the *t*-butyl ester and the lactam functionalities and subsequent decarboxylation provided the GABA derivative **8** in 77% overall yield.

Mechanistic Investigations. Unfortunately, reactions with catalyst **1a** are not optimal under all circumstances. The reactions of nitroalkenes possessing aliphatic-β-substituents **2k**−**n** (Table 2, entries 17−20) or 1,3-diketones **5f** and **5g** as nucleophiles (Table 3, entries 7 and 8) are accompanied by longer reaction times, lower yields, and selectivities relative to those obtained with nitrostyrenes or malonates. To address these deficiencies, we sought a better understanding of the reaction mechanism. Thus, mechanistic studies were initiated on the Michael addition of ethyl malonate to nitrostyrene.

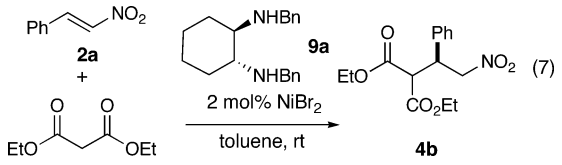
The requirements of the reaction with respect to equivalents of the diamine ligand were examined (Table 4).[24] For example, this addition reaction does not proceed in the absence of ligand (entry 1). Although the reaction proceeds slowly when one equivalent of diamine **9a** (with respect to $NiBr_2$) is employed a good yield is observed (entry 2). Optimal reactivity is observed using two equivalents of ligand **9a** relative to $NiBr_2$ (entry 3). A slower reaction rate and a slight loss in enantioselectivity are observed when excess diamine ligand is utilized (entries 4 and 5). The former can be ascribed to the presence of an uncomplexed ligand that, in turn, decreases the amount of complexed substrate available by biasing the equilibrium in favor of the diamine complex. The slight decrease in selectivity could be attributed to a nonselective background reaction catalyzed solely by uncomplexed free diamine.

To demonstrate that a nonselective background diamine-catalyzed reaction was in operation, the following experiments

(23) For selected reviews, see: (a) *GABA in Nervous System Function*; Roberts, E., Chase, T. R., Tower, D. B., Ed.; Raven Press: New York, 1976. (b) *GABA and Benzodiazepine Receptor subtypes: Molecular Biology, Pharmacology, and Clinical Aspects*; Biggio, G., Costa, E., Ed.; Raven Press: New York, 1990. (c) *GABA in Nervous System Function the View at Fifty Years*; Martin, D. L., Olson, R. W., Ed.; Lippincott Williams & Williams & Wilkins: Philadelphia, PA, 2000.

(24) Nickel(II) bromide and diamine **9a** were stirred in toluene for 1 h at 70 °C before the addition of nitrostyrene **2a** and diethyl malonate **3b**.

Table 4. Survey of Amounts of Diamine Ligand **9a**[a]

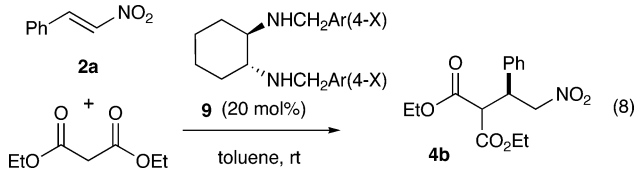


entry	**9a** (equiv against Ni)	time (h)	yield (%)	ee (%)[b]
1	0	36	no reaction	
2	1	36	92	94
3	2	12	93	92
4	3	20	91	90
5	4	22	92	89

[a] All reactions were performed on 0.5 mmol scale at 1 M concentration using 1.2 equiv of diethylmalonate. [b] Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel AD-H column.

were conducted (Table 5). When the reaction was performed with diamine **9a** (20 mol %), 78% yield of the adduct **4b** was obtained with 5% ee (entry 2). It is suspected that this reaction proceeded via deprotonation of the 1,3-dicarbonyl compound by the diamine **9a**, and accordingly anticipated that the addition of polar substituents to the *N*-benzyl ring would suppress this background reaction by making the amine less basic. As expected, when *p*-bromo substituted *N*,*N*′-dibenzyl diamine **9b** was used, the reaction required twice as long to reach completion, indicating that remote polar substituents have a significant effect upon the rate of the background reaction. On the other hand, when *p*-methoxy substituted *N*,*N*′-dibenzyldiamine **9c** was employed, the reaction reached completion faster than in the case of unsubstituted diamine **9a**. Reaction rates are consistent with the basicity of the amines screened, and these results demonstrate that diamine **9** can function as a Bronsted base.

Table 5. The Michael Addition of Diethyl Malonate with Nitrostyrene Catalyzed by Diamine **9**[a]



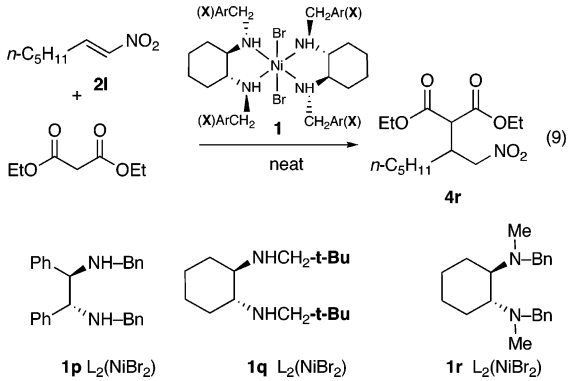
entry	X	time (h)	yield (%)[b]	ee (%)[c]
1	no diamine	36	no reaction	
2	H (**9a**)	72	78	5
3	Br (**9b**)	144	76	0
4	OMe (**9c**)	27	83	6

[a] All reactions were performed on a 0.5 mmol scale at a 1 M concentration using 1.2 equiv of diethylmalonate. [b] Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel AD-H column.

Modification of Nickel Complex 1a. Analogues of catalyst **1a** were investigated in an attempt to limit intrusion of the background reaction, which was suspected to be responsible for the decreased enantioselectivities. The basicity of the ligand would affect not only the rate of deprotonation, of both the complexed and uncomplexed substrate, but possibly also ligand exchange.

Using diethyl malonate and *trans*-1-nitro hept-1-ene (**2l**) as a representative aliphatic nitroalkene, a range of diamine ligands

Table 6. Diamine Ligand Survey for the Addition of Diethyl Malonate to 1-Nitroheptene[a]



entry	X (catalyst)	temp (°C)	time (h)	yield (%)	ee (%)[b]
1	H (**1a**)	room temp	48	84	89
2	H (**1a**)	50	30	75	86
3	*p*-Br (**1g**)	room temp	40	84	87
4	*p*-Br (**1g**)	0	235	73	85
5	*p*-Br (**1g**)	50	9	93	88
6	*o*-Br (**1h**)	50	78	85	85
7	*m*-Br (**1i**)	50	46	80	87
8	*o*-Cl (**1j**)	50	82	87	86
9	*p*-Cl (**1k**)	50	16	76	88
10	*p*-CF_3 (**1l**)	50	42	73	88
11	*p*-NO_2 (**1m**)	50	12	76	88
12	F_5 (**1n**)	50	72	64	76
13	*p*-OMe (**1o**)	50	76	80	85
14	**1p**	50	18	71	89
15	**1q**	50	106	73	27
16	**1r**	50	288	48	46

[a] All reactions were performed on 1 mmol scale with 2 mol % of **1** using 2.0 equiv of diethylmalonate. [b] Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel AD-H column.

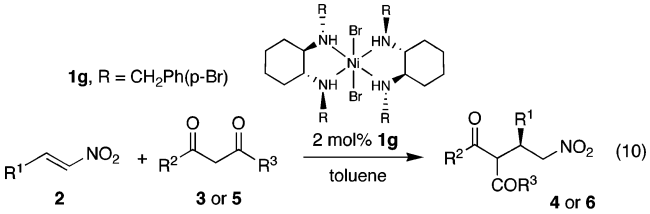
were examined (Table 6).[25] To shorten the reaction times, the majority of experiments were conducted at 50 °C. Under these conditions, utilizing the original catalyst **1a**, the reaction time was reduced by a third while the enantioselectivity was relatively unaffected (entry 2). The less basic *p*-bromo substituted ligand was prepared and provided an improved outcome relative to **1a** at 50 °C (entry 5). Specifically, the reaction was considerably faster and provided a higher yield of **4r** while maintaining high enantioselectivity. A reduction in temperature led to a reduction in yield and dramatically increased reaction times (entries 3 and 4). The diminished yields have been attributed to poor catalyst turnover. Mindful of the acceleration of the reaction rate that resulted from incorporation of the electron-withdrawing bromide group, we prepared other catalysts with polar substituents on the aromatic ring and examined the reaction at 50 °C (entries 6−13). These results demonstrate complex relationship between ligand structure and reaction rate. For example, *o*- and *m*-bromine-substituted analogues **1h** and **1i** were much less effective catalysts (entries 6 and 7), requiring longer reaction times as well as providing lower yields of **4r** relative to **1g**. These observations, also corroborated by the results obtained with the chlorine substituted complexes **1j** and **1k** (entries 8 and 9), indicate a possible adverse steric effect in the transition state of the ortho-substituted analogues. Other electron-withdrawing ligands **1l**−**n** required longer reaction times (entries

(25) All catalysts were prepared and isolated before reactions were performed.

10−12). This suggests that proton abstraction in these cases may be rate limiting, as the corresponding free amine is expected to be less basic. The *p*-methoxy-substituted complex **1o** led to increased reaction time relative to **1g** (entry 13). 1,2-Diphenyl-1,2-diaminoethylene derivative **1p** was less effective (entry 14). The *t*-butyl analogue **1q** and tertiary amine complex **1r** were also examined but did not yield satisfactory results (entries 15 and 16).

Optimized catalyst **1g** (Ar = *p*-bromophenyl) was next examined with substrates that proved problematic in the Michael addition with the original catalyst **1a** (Table 7). In the reactions of β-substituted nitrostyrenes possessing unsaturated side chains, catalyst **1g** was shown to afford similar enantioselectivities and yields to catalyst **1a** (entries 1 and 2). Application of the new catalyst **1g** to alkyl-substituted nitroalkenes, which gave unsatisfactory results with catalyst **1a**, afforded improved yields, enantioselectivities, and dramatically improved reaction times to reach completion (entries 3−5). Catalyst **1g** was demonstrably more successful than catalyst **1a** when used with the more acidic diketone substrates such as acetylacetone and 3,5-heptanedione (entries 6−8). A slight improvement in enantioselectivity was observed with substrate **5f** by performing the reaction in THF (entry 7). Variation in reaction conditions may be necessary to achieve optimal results.

Table 7. Scope of the Michel Addition to Nitroalkene Catalyzed by **1g**[a]

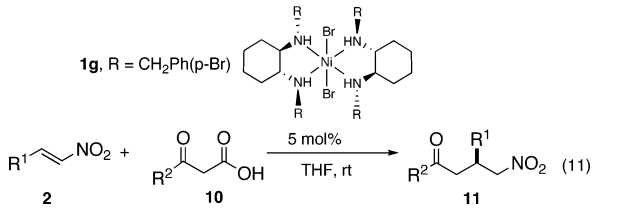


entry	R^1	R^2	R^3	temp (°C)	time (h)	yield (%)	ee (%)[b]
1	Ph (**2a**)	OEt	OEt (**3b**)	room temp	24	99 (**4b**)	95
2	*trans*-PhCH=CH (**2j**)	OEt	OEt (**3b**)	room temp	72	99 (**4p**)	95
3	$Ph(CH_2)_2$ (**2k**)	OEt	OEt (**3b**)	room temp	28	95 (**4q**)	91
4[c]	C_5H_{11} (**2l**)	OEt	OEt (**3b**)	50	9	93 (**4r**)	88
5[d]	Me_2CHCH_2 (**2m**)	OEt	OEt (**3b**)	50	15	92 (**4s**)	90
6	Ph (**2a**)	Me	Me (**5f**)	room temp	18	94 (**6g**)	88
7[e]	Ph (**2a**)	Me	Me (**5f**)	room temp	72	88 (**6g**)	90
8	Ph (**2a**)	Et	Et (**5g**)	room temp	30	91 (**6h**)	92

[a] All reactions were performed on 1 mmol scale with 2 mol % of **1g** at 1 M concentration using 1.2 equiv of the 1,3-dicarbonyl compound. [b] Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel AD-H column. [c] Conducted neat with 2 equiv of diethyl malonate. [d] Conducted at 2 M concentration. [e] Reaction was performed in THF.

***β*-Ketoacid Additions.** While there are two reported examples of Lewis acid-catalyzed enantioselective decarboxylative aldol reactions,[26] to the best of our knowledge, there are no examples of Lewis acid-catalyzed enantioselective decarboxylative Michael additions. As such, the utilization of β-ketoacids in the illustrated Michael additions catalyzed by **1g** was investigated (Table 8). The intermediate adducts were anticipated to undergo decarboxylation under the reaction conditions to provide enantiomerically enriched products. A reaction procedure using THF at room temperature in the presence of 5 mol % catalyst **1g** provided decarboxylative Michael adducts **11** with the best yields and selectivities in a one-pot operation.[27] In this system, nitrostyrenes possessing an electron-deficient β-aryl substituent **2d** (R^1 = 4-Br−Ph) yielded the best results (entry 3). However, diminished yields and enantioselectivities were observed with substrates **2j** and **2l** (entries 5 and 6). Electron-donating groups on the aromatic ring **10b** and **10c** at the Michael donor (entries 7and 8) are well tolerated, whereas electron-withdrawing **10d** substituents dramatically reduce the rate of the addition reaction (entry 9).

Table 8. Scope of the Michel Addition of β-Ketoacids to Nitroalkene Catalyzed by **1g**[a]



entry	R^1	R^2	time (h)	yield (%)	ee (%)[a]
1	Ph (**2a**)	Ph (**10a**)	24	95 (**11a**)	90
2	4-Me−Ph (**2b**)	Ph (**10a**)	38	87 (**11b**)	88
3	4-Br−Ph (**2d**)	Ph (**10a**)	21	99 (**11c**)	94
4	3,4-OCH_2O−Ph (**2h**)	Ph (**10a**)	80	77 (**11d**)	90
5	*trans*-Ph−CH=CH (**2j**)	Ph (**10a**)	115	50 (**11e**)	80
6	*n*-C_5H_{11} (**2l**)	Ph (**10a**)	160	51 (**11f**)	77
7	Ph (**2a**)	4-MeO−Ph (**10b**)	36	80 (**11g**)	90
8	Ph (**2a**)	3-MeO−Ph (**10c**)	45	89 (**11h**)	90
9	Ph (**2a**)	4-F−Ph (**10d**)	138	81 (**11i**)	87

[a] All reactions were performed on 0.25 mmol scale with 5 mol % of the preformed catalyst **1g** at 0.17 M concentration using 1.2 equiv of the β-ketoacid. [b] Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel AD-H column.

Evidence of Proton Abstraction by the Diamine Ligand. Having established various elements within the catalyst structure that control reaction rates, yields, and selectivities, attention was turned to investigation of the mechanism. NMR spectroscopic experiments were performed upon the Ni catalyst **1g** in $CDCl_3$ (Figure 3). The ^{1}H NMR spectrum of nickel complex **1g** contains relatively broad peaks owing to the paramagnetic character of nickel(II) (spectrum a in Figure 3). However, when one equivalent of acetylacetone was added to complex **1g** new signals appeared in both the ^{1}H and ^{13}C NMR spectra, indicating that a ligand displacement had occurred (spectrum b in Figure 3). Spectrum b bears greater similarity to spectrum c, the HCl salt of diamine **9b**, which is the ligand within complex **1g**, than spectra d diamine **9b** itself. It can be concluded that in the presence of acetylacetone one of the diamine ligands is fully displaced from catalyst **1g** by the substrate and the liberated diamine then deprotonates the metal-bound acetylacetone. It should be noted that the catalyst−acetylacetone complex cannot be observed due to the paramagnetic character of Ni(II) to which it is complexed, thus only the noncomplexing ammonium species is observed. This experiment confirms the hypothesis that the diamine ligand is indeed displaced by the substrate and thus can serve as the necessary base for the enolization event.

(26) (a) Orlandi, S.; Benaglia, M.; Cozzi, F. *Tetrahedron Lett.* **2004**, *45*, 1747. (b) Magdziak, D.; Lalic, G.; Lee, H. M.; Fortner, K. C.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 7284.

(27) Catalyst **1a** gave both lower reactivity and selectivity (48 h, 83%, 90% ee). All reactions proceeded with loss of yield and enantioselectivity in other solvents: CH_2Cl_2 (44%, 28% ee), toluene (41%, 52% ee), ethyl acetate (44%, 61% ee), 1,4-dioxane (90%, 88% ee), diethylether (80%, 82% ee), acetonitrile (31%, 67% ee), and ethanol (47%, 63% ee).

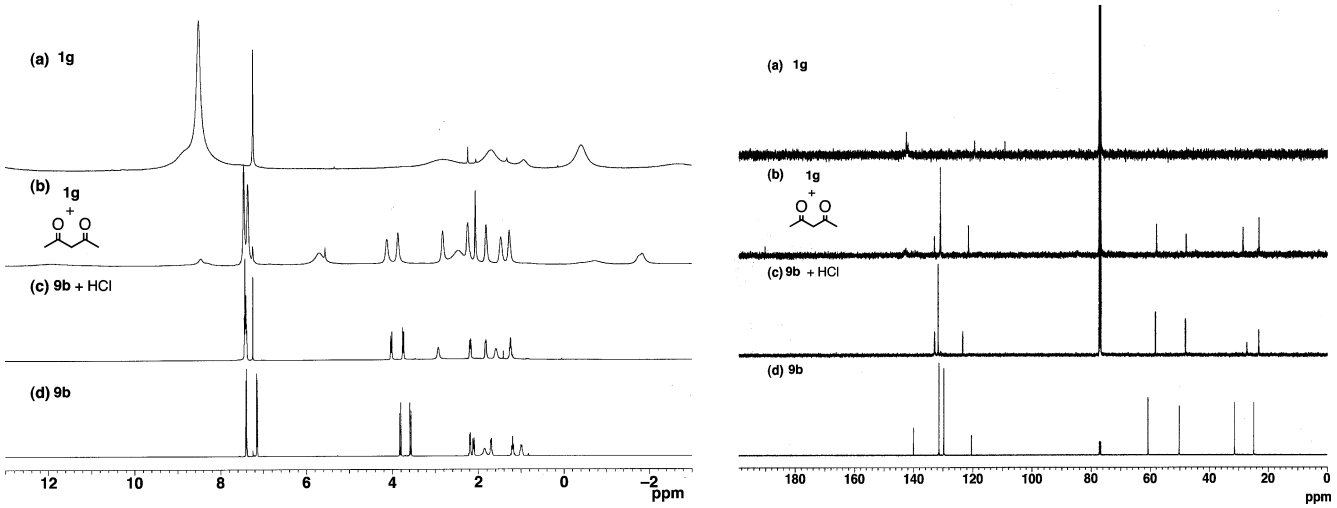
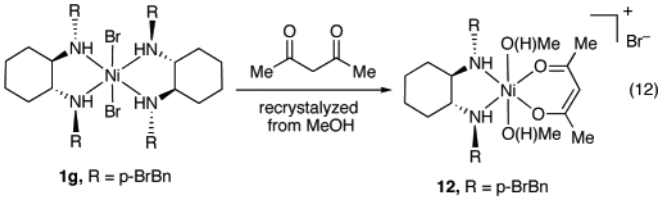


Figure 3. ^{1}H and ^{13}C NMR spectra in $CDCl_3$: (a) nickel complex **1g**; (b) 1:1 mixture of nickel complex **1g** and acetylacetone; (c) diamine **9b** hydrochloride; (d) diamine **9b**.



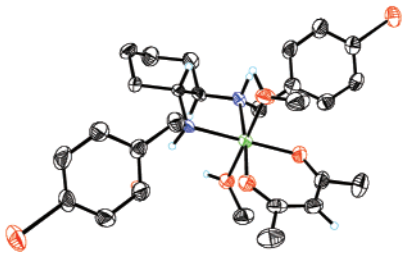


Figure 4. The ORTEP diagram of complex **12**.

A Stereochemical Model. Single crystals of catalyst−substrate complex **12** were isolated and subjected to X-ray analysis in an attempt to gain direct evidence for the existence of the proposed intermediate (eq 12). The ORTEP diagram of complex **12** is shown in Figure 4. The nickel exhibits octahedral geometry with the chiral diamine ligand and enolate occupying the equatorial plane of the complex. Molecules of methanol occupy each apical position and one bromide ion acts as a counterion. As the conditions in which the complex was generated mirror the reaction conditions, it seems likely that only one diamine ligand is displaced during the reaction. It is presumed that the apical positions are occupied either by bromide ions or water, or one of each, under the reaction conditions.

This crystal structure of catalyst−substrate complex **12** can be used to rationalize the sense of stereoinduction observed in the addition reaction (Figure 5). One can assume that in the transition state the incipient nitronate anion is stabilized by interaction at the open apical position on the nickel. In the disfavored transition state (pro *R* addition), the nitro moiety of the electrophile faces steric interactions with the *N*-benzyl group of the ligand. On the other hand, in the favored transition state (pro *S* addition), the *N*-benzyl group of the ligand is orientated away from the electrophile.

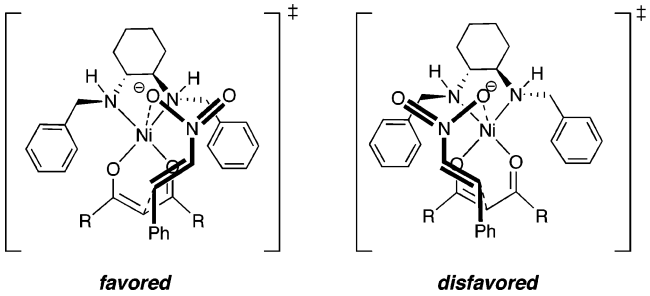
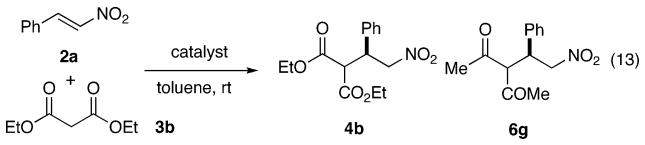
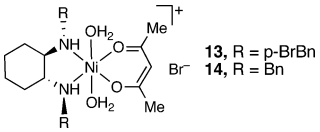


Figure 5. Transition-state models for the Michael addition with nitrostyrene.

Table 9. Catalyst−Substrate Complex in the Michael Addition[a]



			4b		6g	
entry	catalyst	time (h)	yield (%)	ee (%)[b]	yield (%)	ee (%)[b]
1	**13** (2 mol %)	18	98	94		
2	**14** (2 mol %)	32	86	96		
3	**14** (20 mol %)	10	89	94	2	45
4	**14** (100 mol %)	7	97	82	3	66



[a] All reactions were performed on 0.25 mmol scale at 0.5 M concentration using 1.2 equiv of diethylmalonate. [b] Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel AD-H column.

The diamine−acetylacetone complexes **13** and **14** were investigated as the catalysts in the addition reaction of diethyl malonate **3b** to nitrostyrene **2a** (Table 9).[28] The reaction proceeded smoothly to deliver **4b** in good yield with high enantioselectivity in the presence of 2 mol % of complex **13**. The addition reaction with 2 mol % **14** required 32 h and

(28) Catalysts **13** and **14** were prepared from the nickel bisdiamine complexes with 1 equiv of acetylacetone and isolated before reactions were performed. See Supporting Information.

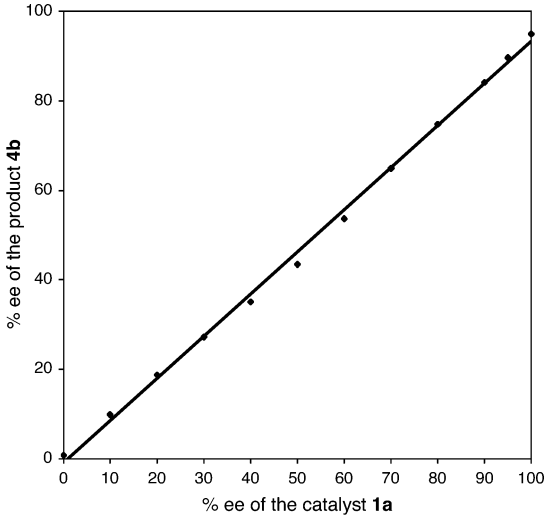


Figure 6. Nonlinear effects in the Michael addition of diethyl malonate to nitrostyrene catalyzed by **1a**.

generated **4b** in 86% yield with 96% ee (entry 2). Similar yields and enantioselectivities of **4b** were observed in the presence of 20 mol % **14** relative to the reaction that was performed with 2 mol % **14** (entry 3). However, acetylacetone adduct **6g** was also isolated in 2% yield (45% ee). Even the reaction with 100 mol % of **14** gave **6g** in 3% yield (66% ee) with **4b** in 97% yield (82% ee). Thus, it appears that the acetylacetone ligand in **14** can be displaced by diethyl malonate[29] and the liberated acetylacetone can then undergo a less selective reaction to provide product **6g**.

Given that this process can occur in the absence of additional base, the substrate *itself* is believed to act as a proton source to facilitate decomplexation of the Michael adduct. This is in contrast to standard soft enolization scenarios, wherein the conjugate acid of the ancillary base is believed to behave as a proton donor in the final step.[19]

The reaction between diethyl malonate and nitrostyrene, catalyzed by the parent $NiBr_2$-diamine complex **1a** was next probed for nonlinear effects.[30] As the data in Figure 6 indicate, the linear relationship between enantiomeric excess and catalyst ee reveals that the active catalyst may be a monomeric species. This result is consistent with our kinetic studies that show that the reaction is first order in metal complex (vide infra).

To further probe the reaction mechanism, kinetic studies of the addition reaction of diethyl malonate to nitrostyrene with catalyst **1a** monitored by ^{1}H NMR was performed. In the presence of an excess of diethyl malonate in the reaction, the plot of ln([nitrostyrene]/[nitorostyrene^0]) versus time showed a linear relationship ($R^2 = 0.9849$, Figure 7A), indicating first-order dependence on nitrostyrene. In a similar manner, when excess nitrostyrene was employed, the reaction was first-order in diethyl malonate ($R^2 = 0.9906$, Figure 7B). In addition, within the first 45 min, the reaction proceeded relatively slowly, but afterward in both instances the substrate was consumed at a constant rate. This implies that the ligand exchange step from **1** to **A** is slow and reversible (see Scheme 2). The complexation of the nitrostyrene presumably represents the rate-determining step in this catalytic cycle (**A** to **B**). After the rapid-bound enolate addition to the bound nitrostyrene (**B** to **C**) the subsequent deprotonation of the catalyst bound dicarbonyl species completes this catalytic cycle (**C** to **A**).

Reaction Mechanism. On the basis of the results presented above, we propose the mechanism shown in Scheme 2. First, a dicarbonyl substrate displaces a diamine ligand, which in turn deprotonates the metal-bound substrate to generate the chiral enolate **A**. Complexation of the nitrostyrene on the apical position (**B**) followed by nucleophilic attack of the bound enolate to the bound nitrostyrene results in formation of the complex **C**. Displacement of the product with a dicarbonyl substrate with concurrent deprotonation regenerates enolate **A** in the catalytic cycle.

Development of a Nickel(II) Monodiamine Catalyst. Given that the data suggest the active catalyst contains only one diamine ligand, monodiamine complex **15** was prepared as a potential new catalyst. The ORTEP diagram of the tetrahedral complex **15** is shown in Figure 8.

Nickel(II) monodiamine complex **15** was subsequently evaluated as a catalyst for the Michael addition of diethyl malonate to nitrostyrene (Table 10). Although high enantioselectivity was achieved, the reaction was found to be sluggish when performed with 2 mol % of **15** (75% conversion, 42 h, entry 1). However, when the addition reaction was performed in the presence of diamine ligand **9a**, product **4b** was obtained in good yield and high enantioselectivity with a decreased reaction time (entry 2). Generation of nickel catalyst **1a** in situ under these conditions was strongly suspected. Furthermore, when racemic **9a** was used the enantioselectivity dropped significantly, an observation that is consistent with the formation of a racemic catalyst (entry 3).

We speculate that the inefficiency of catalyst **15** may be attributed to its tetrahedral geometry (Figure 8). An octahedral geometry of the nickel catalyst was presumed to be required in

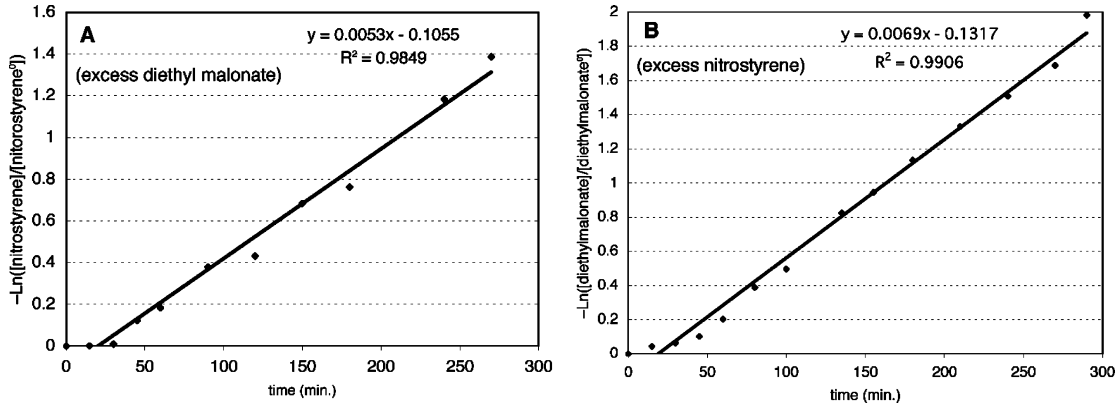


Figure 7. Kinetic studies on the addition of diethyl malonate to nitrostyrene: (A) excess diethyl malonate; (B) excess nitrostyrene.

Scheme 2. Proposed Reaction Mechanism

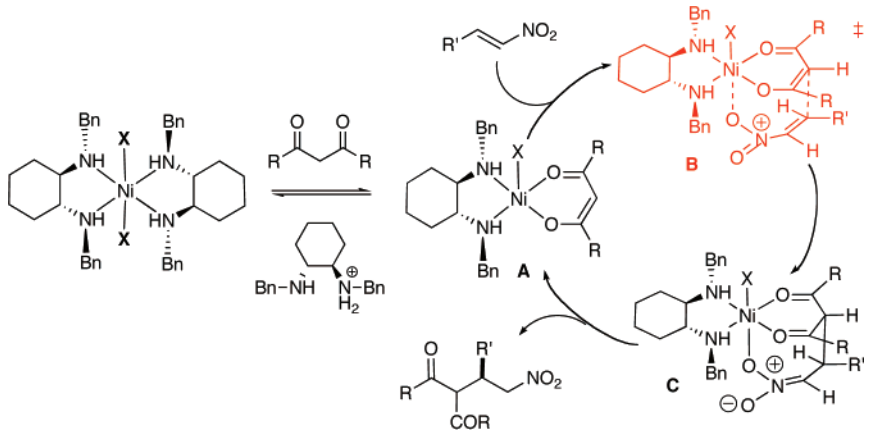
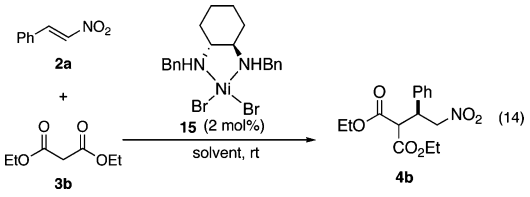


Table 10. Diamine-Catalyzed Michael Addition of Diethyl Malonate to Nitrostyrene[a]



entry	catalyst	additive	time (h)	yield (%)	ee (%)[b]
1[c]	toluene		42	70	95
2	toluene	**9a** (2 mol %)	9	82	95
3	toluene	**9a** (racemic, 2 mol %)	10	93	12
4	toluene	H2O (11 mol %)	10	99	94
5	toluene	Et3N (4 mol %)	135	52	84
6	toluene	MS 4A (25 mg)	24	91	94
7	THF	H2O (11 mol %)	115	90	91
8	MeOH	–	50	78	61
9	EtOH	–	140	72	66

[a] All reactions were performed on 0.25 mmol scale at 0.5 M concentration using 1.2 equiv of diethylmalonate. [b] Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel AD-H column. [c] Conversion = 75%.

this reaction to facilitate catalyst turnover. If this hypothesis were operative, introduction of two apical ligands to the square planar complex would satiate the structural requirements of the catalyst. As anticipated, the addition of 5.5 equiv of water with respect to the catalyst significantly increased the reaction rate and provided the Michael adduct **4b** in quantitative yield with high enantioselectivity (entry 4).

To gain information of the coordination state, single crystals of **15** with water were accessed and subjected to X-ray analysis, but it was unstable under air and the analysis failed to give data of sufficient quality. However the structure was tentatively

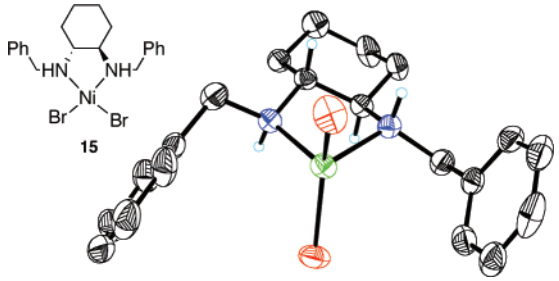
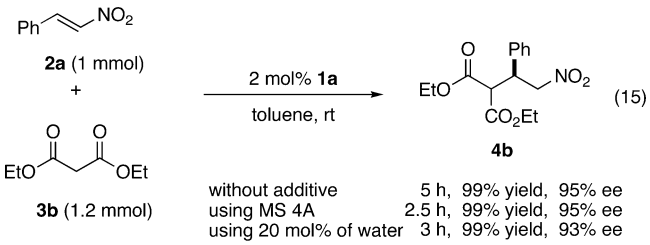


Figure 8. The ORTEP diagram of complex **15**.

assigned octahedral geometry, and two diamines and two water molecules completed a bisaqua nickel complex. This suggests that in the reaction the active nickel species is an bisaqua complex and it works more efficiently to generate the enolate.[31] The addition of 4 Å molecular sieves (MS 4 Å) was also found to accelerate the addition reaction while maintaining high yields and enantioselectivity (entry 6). On the other hand, when 2 equiv of Et_3N relative to the catalyst were used, the reaction was sluggish and diminished yield and enantioselection were observed (entry 5). This could be due to the improved donor properties of the amine relative to the alcohol such as methanol and ethanol (entries 8 and 9). A dramatic solvent effect was also observed. When THF was used as the solvent, in the presence of 5.5 equiv of water relative to the catalyst, both the yield and enantioselectivity were reduced relative to the reaction in toluene (entry 7). This effect was even more apparent when methanol and ethanol were used as the solvents; yields and enantioselectivities both suffered a diminution (entries 8 and 9). The alcoholic solvents are suspected of preferentially occupying the apical sites on the nickel, and thus inhibit the nitrostyrene from binding to the catalyst−substrate complex. To further evaluate this trend, we examined the reaction with **1a** in the presence of 4 Å molecular sieves or water and similar results were observed (eq 15).



These results demonstrate that water modestly retards the reaction. We speculate that water could be coordinating to the metal center and retarding the turnover step. Although there is no evidence that the molecular sieves directly interact with the

(29) $Ni(acac)_2$ was found to be an effective catalyst for Michael additions of 1,3-dicarbonyl compounds. It was confirmed that acetylacetones within Ni(acac)$_2$ were replaced by β-dicarbonylates to generate Ni(β-dicarbonylate)$_2$, see: (a) Nelson, J. H.; Landen, G. L.; Stevens, B. N. *Synth. React. Inorg. Met.-Org. Chem.* **1979**, *9*, 435. (b) Nelson, J. H.; Howells, P. N.; DeLullo, G. C.; Landen, G. L.; Henry, R. A. *J. Org. Chem.* **1980**, *45*, 1246. (c) Fei, C. P.; Chan, T. H. *Synthesis* **1982**, 467.
(30) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1997**, *37*, 2923.
(31) Palladium bisaqua and hydroxo complexes were found to be effective for enolization of 1,3-dicarbonyl compounds, see ref 7a.

catalyst, this additive could facilitate either product diamine ligand exchange[32] or formation of the active nickel species relevant to the acceleration of the enolization step.[33]

Conclusions

In summary, a direct, catalytic, enantioselective Michael addition of 1,3-dicarbonyl compounds to nitroalkenes that is conveniently performed under ambient temperature without the need to exclude air or moisture has been developed. The catalyst design is centered on a Lewis acid metal complexed by two chiral diamine ligands that are able to fulfill a dual role. Notable features of this reaction are its operational simplicity and the obviated prerequisite for addition of an external base. Mechanistic studies support a monomeric catalyst that undergoes ligand exchange and subsequent activation of the dicarbonyl compound via enolization by the liberated diamine ligand. The resulting chiral enolate adds enantioselectively to a broad range of nitroalkenes. Furthermore, a monodiamine catalyst analogue can be used for this reaction in the presence of water.

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Supporting Information Available: Experimental procedures, spectral data for all compounds, and stereochemical proofs; CIF files of **12** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) The ligand exchange from $(^{i}PrO)_2TiCl_2$ to $(BINOL)_2TiCl_2$ is facilitated in the presence of molecular sieves, see; (a) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem, Soc.* **1994**, *116*, 2812. (b) Mikami, K. *Pure Appl. Chem.* **1996**, *68*, 639.

(33) Pd-hydroxo species was formed from Pd bisaqua complexes in wet acetone in the presence of molecular sieves and the Pd-OH plays a beneficial role as a Bronsted base in the enolization step, see ref 32 and the following: Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450.