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Enantioselective Michael Additions of Nitromethane by a Catalytic Double Activation Method Using Chiral Lewis Acid and Achiral Amine Catalysts

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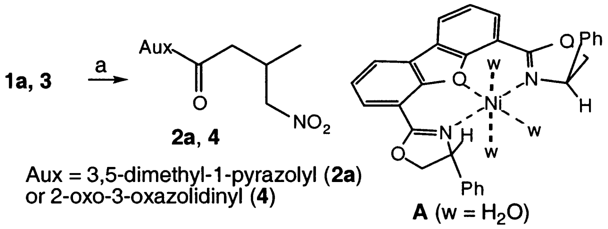
Chiral Lewis acid-catalyzed enantioselective reactions provide one of the most powerful and economical synthetic approaches leading to a variety of enantiomers. Generally, electrophiles are activated by coordination to a chiral Lewis acid catalyst, and nucleophiles react preferentially with the resulting enantiopure electrophile/catalyst complexes to give enantiomerically enriched products. When reactivity of nucleophiles is not sufficiently high enough to react smoothly with the electrophiles activated by coordination to the catalyst, effective enantiomer formation becomes difficult. Although additional activation of the nucleophiles by use of a base catalyst would be a possible solution, such combined use of two catalysts should cause a serious problem such that acid and base catalysts strongly bind each other, resulting in the disappearance of catalytic capability. Success would be realized only when both the catalysts show separate catalytic activities when they are used together in one flask.[1]

We have effective chiral Lewis acid catalysts in hand, which are the cationic aqua complexes derived from (*R*,*R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) (*R*,*R*-DBFOX/Ph hereafter)[2] and transition metal salt hydrates having noncoordinating anionic counterions. One of the most important features of these aqua *R*,*R*-DBFOX/Ph complexes is high tolerance toward strongly nucleophilic substrates. Although highly coordinating nucleophiles do bind with the metallic center of the catalyst, the binding should be relatively weak to undergo rapid ligand exchange between such strong nucleophiles and electrophilic substrates.[3] Thus, the transition metal aqua complexes of *R*,*R*-DBFOX/Ph show highly effective chirality control in cyclopentadiene Diels−Alder reactions even in the presence of a variety of amine additives.[4] Accordingly, the *R*,*R*-DBFOX/Ph aqua complexes would be the chiral Lewis acid catalysts of our choice for the double activation method by use of both Lewis acid and base catalysts.[5]

In this communication, we report a new synthetic methodology for catalytic enantioselective Michael addition reactions of nitromethane.[6] Therein, both α,*β*-unsaturated carbonyl acceptors as electrophiles and nitromethane as nucleophile can be activated by catalytic amounts of chiral Lewis acid and amine catalysts, respectively. We propose this new catalytic method leading to enantiomers of products to be named "*catalytic double activation method (CDAM)*".[1,5]

Scheme 1 [a]



1 / 3	Conditions	Product	Time/h	Yield/%	ee/%
1a	MeNO$_2$ (1 equiv) in THF	**2a**	168	trace	-
1a	MeNO$_2$ as solvent	**2a**	5	95	77
1a	MeNO$_2$ in THF (1:1 v/v)	**2a**	5	97	84
1a	MeNO$_2$ in THF (1:1 v/v)/ MS 4A	**2a**	5	84	67
3	MeNO$_2$ as solvent	**4**	144	30	39

[a] a: In the presence of **A** and TMP (10 mol % each), rt.

The reaction between nitromethane and 1-crotonoyl-3,5-dimethylpyrazole (**1a**) was successfully induced in the presence of *R*,*R*-DBFOX/Ph·Ni(ClO$_4$)$_2$·3H$_2$O (**A**) and 2,2,6,6-tetramethylpiperidine (TMP), both in catalytic amonts (10 mol %), in nitromethane to give 3-methyl-4-nitrobutanoyl-3,5-dimethylpyrazole (**2a**) as Michael adduct in 95% yield (77% ee) after 5 h at room temperature (Scheme 1). Although TMP as amine catalyst catalyzes the above reaction by itself (10 mol %, rt, 72 h, 89%),[7] **A** as Lewis acid shows no catalytic activity. An even more obvious example for the high activation of the nitromethane conjugate addition under CDAM conditions is the reaction with *β*-phenyl-substituted pyrazole **1k** as acceptor: The adduct **2k** was obtained in only 5% yield after 168 h at room temperature when the reaction was catalyzed only by TMP (10 mol %), while the same reaction under CDAM conditions, even at −20 °C, gave adduct **2k** in 90% yield (93% ee). *Thus, the combined use of Lewis acid and amine catalysts works in a highly effective manner to accelerate Michael addition reactions with nitromethane.*

Under the optimized conditions, the reaction of nitromethane with **1a** was performed in a 1:1 vol/vol mixture of nitromethane and THF at room temperature (5 h) in the presence of 10 mol % each of **A** and TMP to give **2a** in 97% yield with an enantioselectivity of 84% ee (Scheme 1).[8,9] As the Lewis acids, the *R*,*R*-DBFOX/Ph complex derived from Ni(ClO$_4$)$_2$·6H$_2$O was the most effective catalyst,[10,11] and the aqua complex **A** showed both a much higher reactivity and greater selectivity than the anhydrous complex catalyst *R*,*R*-DBFOX/Ph·Ni(ClO$_4$)$_2$ (rt, 48 h, **2a**: 19%, 31% ee). The same reaction catalyzed by **A** in the presence of MS 4A gave **2a** in 84% yield (67% ee). Although a variety of amine catalysts could be utilized effectively, 2,2,6,6-tetramethylpiperidine (TMP) as bulky amine gave the best balance of the catalytic activity and enantioselectivity.[12] The reaction using 3-crotonoyl-2-oxazolidinone (**3**) was much less reactive than the pyrazole substrate **1a**, indicating that the pyrazole acceptors **1** derived from 3,5-dimethylpyrazole were needed (Scheme 1).

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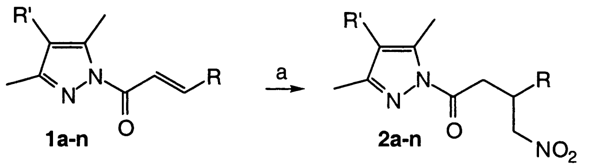
Scheme 2 [a]

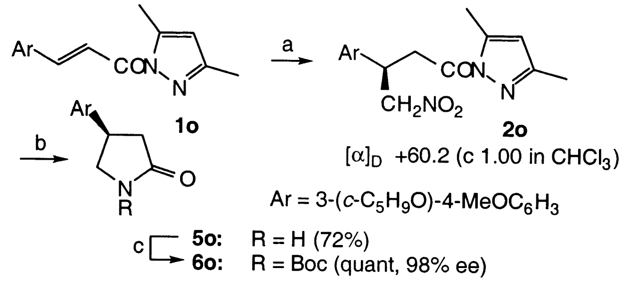


1a-n **2a-n**

1 / 2	R	R'	Temp/°C	Time/h	Yield/%	ee/%
a	Me	H	rt	5	97	84
a		H	0	48	91	90
a		H	-20	96	85	94
b		Br	-20	96	97	95
c		I	-20	96	62	96
d	Et	H	0	24	93	94
e	*n*-Pr	H	-20	96	96	91
f	*i*-Pr	H	-20	168	74	97
g	*c*-Hex	H	-20	168	90	91
h	*t*-Bu	H	0	168	39	95
i	(*E*)-MeCH=CH-	H	-20	96	49	77
j	MeOOC	H	rt	3	91	83
k	Ph	H	-20	168	90	93
l	3,4-(OCH$_2$O)C$_6$H$_3$	H	-20	168	77	98
m	2-Furyl	H	-20	96	75	97
n	2-Thienyl	H	-20	168	83	97

[a] a: **A** and TMP (10 mol % each) in MeNO$_2$/THF (1:1 v/v).

Scheme 3 [a]



1o

2o

$[\alpha]_D$ +60.2 (c 1.00 in CHCl$_3$)

Ar = 3-(*c*-C$_5$H$_9$O)-4-MeOC$_6$H$_3$

5o: R = H (72%)

6o: R = Boc (quant, 98% ee)

[a] a: *R*,*R*-DBFOX/Ph − Ni(ClO$_4$)$_2$·6H$_2$O (10/10 mol %), TMP (10 mol %), MeNO$_2$/THF (1:1 v/v, 0.1 M), −20 °C, 168 h, 91%. b: H$_2$ Raney Ni, EtOH/CH$_2$Cl$_2$ (3:2 v/v (0.06 M), 1 atm, rt, 96 h. c: (Boc)$_2$O and 4-DMAP (2 equiv each), Et$_3$N (1 equiv), rt, 12 h.

Finally, Michael additions of nitromethane with 1-(2-alkenoyl)-3,5-dimethylpyrazoles (**1a**−**n**) having a variety of β-substituents were found to take place smoothly under the standard conditions at −20 °C to produce the Michael adducts **2a**−**n** (Scheme 2). Enantioselectivities up to 98% ee were observed. Acceptor substrates **1a**−**h** with methyl and primary to tertiary alkyl substituents could be applied successfully, although acceptor **1h** with a bulky *tert*-butyl substituent is much less reactive. Other β-substituents such as 1-alkenyl, ester, aryl, heteroaryl moieties work effectively.

Synthetic potential of this new methodology of nitromethane conjugate additions under CDAM conditions could be demonstrated successfully in the effective and short step synthesis of (*R*)-(−)-rolipram (**5o**)[13] known as an antidepressant and phosphodiesterase inhibitor (Scheme 3). The desired starting substrate **1o** was synthesized by Wittig−Horner olefination of the substituted benzaldehyde, followed by transformation to the pyrazole amide in two steps. The optical yield of the Michael adduct **2o** was determined to be 98% ee after its reductive conversion to (*R*)-rolipram **5o** followed by acylation to the *N*-Boc pyrrolidinone derivative **6o**. The absolute configuration of **5o** was determined on the basis of the reported optical rotation,[13,14] indicating that the *Re*-faces of **1o** have been involved in the carbon−carbon bond-formation step.

In conclusion, the authors have presented a new synthetic methodology for the enantioselective Michael addition reaction of nitromethane under catalytic double activation (CDAM), in which both α,β-unsaturated carbonyl acceptors and nitromethane can be effectively activated by catalytic amounts of chiral Lewis acids and amine catalysts. For this purpose, the high tolerance of the *R,R*-DBFOX/Ph aqua complex catalyst derived from nickel(II) perchlorate hexahydrate toward amine bases as well as an effective chirality induction was essential. Other related reactions along this line are in progress in our group.

Supporting Information Available: Experimental procedure and spectral data of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The addition reaction in nitromethane/THF (1:1 vol/vol) in the presence of **A** and TMP (10 mol % each) is called "standard conditions" hereafter.

(9) One advantage in the use of THF as cosolvent is that the preparation of catalyst **A** from the ligand and Ni(ClO$_4$)$_2$·6H$_2$O can be completed in a few minutes at room temperature.[4a]

(10) The *R,R*-DBFOX/Ph complex derived from Co(ClO$_4$)$_2$·6H$_2$O showed a little higher selectivity, but a lower activity (rt, 144 h, **2a**: 36%, 86% ee).

(11) Other *R,R*-DBFOX/Ph complex catalysts derived from the following salts did not show any catalytic activity: Zn(ClO$_4$)$_2$·6H$_2$O, Cu(ClO$_4$)$_2$·6H$_2$O, Mg(ClO$_4$)$_2$·6H$_2$O, Zn(OTf)$_2$, Cu(OTf)$_2$, and Mg(OTf)$_2$.

(12) See Supporting Information.

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(14) *R*)-(−)-Rolipram (**5o**) was purified by crystallization from AcOEt/hexane (>99% ee). $[\alpha]_D$ −33.9° (*c* 1.09, MeOH) (Lit.[14] $[\alpha]_D$ −31.1° (*c* 1.08, MeOH)).

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