J|A|C|S COMMUNICATIONS

Published on Web 03/03/2010

Diastereo- and Enantioselective Conjugate Addition of α-Ketoesters to Nitroalkenes Catalyzed by a Chiral $Ni(OAc)_2$ Complex under Mild Conditions

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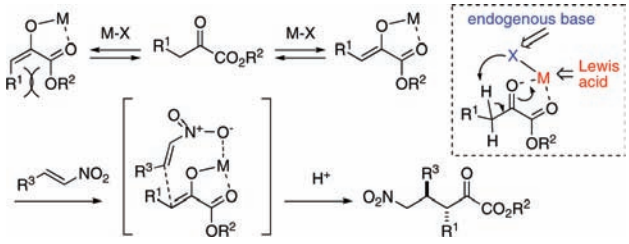
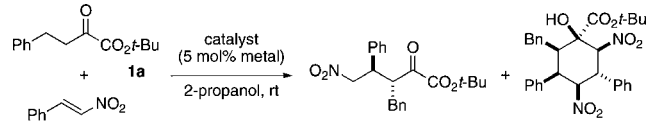
Because of the high potential to rapidly increase molecular complexity as well as the rich chemistry of the nitro group,[1] catalytic diastereo- and enantioselective conjugate addition of carbon pronucleophiles to nitroalkenes has attracted much attention.[2] While pyruvic acid, a representative 1,2-dicarbonyl compound, is an important C2 and C3 donor unit in biosynthesis, related α-ketoesters have rarely been used as nucleophiles in asymmetric catalysis.[3] This is probably because they are considered to be less acidic than 1,3-dicarbonyl compounds and because the high reactivity of α-ketoesters as electrophiles may limit their use as pronucleophiles. Furthermore, the precedent examples[3] often had to use excess reagents and relatively high catalyst loadings. Therefore, the development of selective and active catalysts is desirable. We report herein a highly efficient, catalytic, diastereo- and enantioselective conjugate addition of α-ketoesters to nitroalkenes (Scheme 1).[4] We expected that mild activation by metal complexes with an endogenous basic counteranion might cleanly give a chiral metal enolate with a specific geometry, and its assembly with nitroalkenes would promote the reaction in a stereoselective manner.

Scheme 1. Conjugate Addition of α-Ketoesters to Nitroalkenes



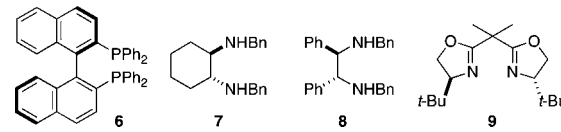
Initially, we examined various metal complexes (Table 1). [Pd{(*R*)-BINAP}(μ-OH)]$_2$(OTf)$_2$ (**5**), developed by us as a mild Brønsted base for the activation of 1,3-dicarbonyl compounds, did not promote the model reaction of **1a** with **2a**.[5,6] Expecting that acetate anion can act as an endogenous base,[7] we next examined several metal acetates. For the catalyst screening, we chose 2-propanol as the solvent because of the increasing need for the use of environmentally friendly solvents. While BINAP complexes were not effective (entries 2 and 3), better results were obtained using diamines as the ligand (entries 4−8). Among them, the 1:1 $Ni(OAc)_2$−**7** complex was found to be the most effective catalyst. Thus, in the presence of 5 mol % Ni catalyst, the reaction reached completion within 4 h at room temperature to afford the product **3a** in 82% yield with 92% ee (entry 6).[8] This reaction was highly product-selective, and no appreciable amounts of the syn diastereomer and overreacted cyclic compound **4a** were detected (<1%). In contrast, a similar Cu complex gave **4a** in a considerable amount (entry 4). Interestingly, as shown in entry 9, the 1:1 $NiBr_2$−**7** complex did not catalyze the reaction at all, clearly indicating that the acetate anion plays an important role in our reaction.[9]

Table 1. Optimization of the Reaction Conditions



			yield (%)[a] [% ee][b]	
entry	catalyst	time (h)	**3a**	**4a**
1	Pd complex **5**	48	trace	−
2[c]	$Pd(OAc)_2$ + **6** (1:1)	48	18 [−85]	23
3[c]	$Ni(OAc)_2$·$(H_2O)_4$ + **6** (1:1)	48	75 [0]	8
4[c]	$Cu(OAc)_2$·$(H_2O)_2$ + **7** (1:1)	4	43 [−21]	23 [−22]
5[c]	$Zn(OAc)_2$·$(H_2O)_2$ + **7** (1:1)	24	43 [90]	<1
6[c]	$Ni(OAc)_2$·$(H_2O)_4$ + **7** (1:1)	4	**82 [92]**	<1
7[c]	$Ni(OAc)_2$·$(H_2O)_4$ + **8** (1:1)	4	81 [32]	8 [38]
8[c]	$Ni(OAc)_2$·$(H_2O)_4$ + **9** (1:1)	24	50 [55]	18 [55]
9[d]	$NiBr_2$−**7**	50	trace	−
10[d]	$Ni(OAc)_2$−**7** (1 mol %)	24	58 [93]	18 [83]
11[d]	entry 10 + Et_3N (5 mol %)	4	**86 [92]**	5 [76]
12[d]	$Ni(OAc)_2$−**7** (**0.1 mol %**) + Et_3N (2 mol %)	4	**81 [92]**	not determined

[a] Isolated yield based on **1a**. [b] Determined by chiral HPLC analysis. [c] The catalyst was prepared in situ. [d] The isolated 1:1 Ni−ligand complex was used.



Although the reaction was slow with 1 mol % Ni catalyst, the addition of a small amount of Et_3N was found to be effective (entries 10 and 11).[10] Furthermore, as little as 0.1 mol % Ni complex was sufficient to promote the reaction efficiently without any loss of enantioselectivity (entry 12). On the basis of the results with the $NiBr_2$ and $Ni(ClO_4)_2$ complexes,[9] the acetate anion is considered to act as the primary base, and the added triethylamine likely traps the acetic acid generated to facilitate the formation of the enolate,

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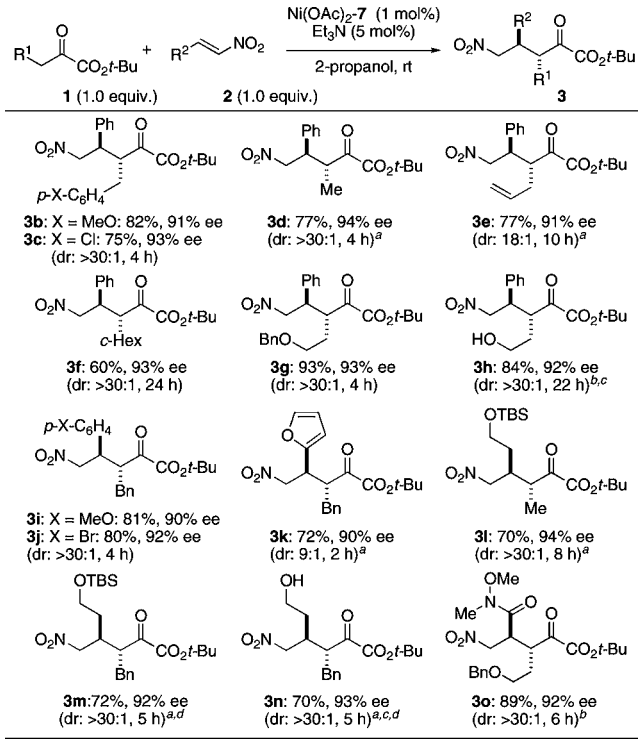
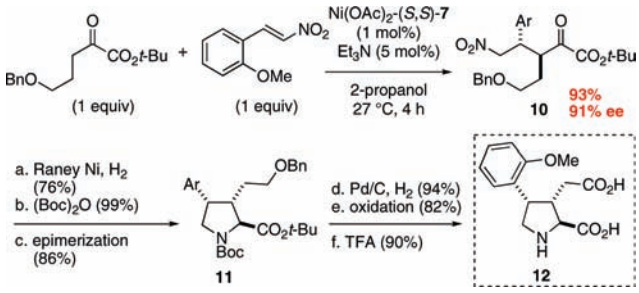
10.1021/ja909457b

Chart 1. Generality of the Reaction



Isolated yields are for the major diastereomers. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude products. [a] Using 1.5 equiv of **1**. [b] Using 5 mol % Ni complex without Et_3N. [c] The product was isolated as its intramolecular hemiacetal. [d] Using 5 mol % Ni complex and 5 mol % Et_3N.

Scheme 2. Application to the Synthesis of Kainoid Analogue **12**[a]



[a] Conditions: (a) Raney Ni, H_2, EtOH, 75 °C, 4 h; (b) $(Boc)_2O$, Et_3N, rt, 0.5 h; (c) NaH, DBU, *t*-BuOH, benzene, rt, 18 h; (d) Pd/C, H_2, THF, rt, 3 h; (e) Dess−Martin oxidation followed by $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O; (f) TFA, CH_2Cl_2, rt, 2 h.

which is particularly important when the catalyst amount is small. The relative and absolute stereochemistries of the major product **3a** were unequivocally determined by X-ray analysis.[11,12]

Having established the optimized conditions, we next examined the scope of the reaction. As shown in Chart 1, this reaction displayed broad generality with respect to α-ketoesters and nitroalkenes. In most cases, the reaction reached completion within several hours at room temperature, and the desired product was obtained in a highly stereoselective manner (dr = >30:1, up to 94% ee). Since our reaction conditions are mild, acid- or base-sensitive functional groups were well-tolerated, and even an unprotected hydroxyl group could be used without difficulty (e.g., **3h** and **3n**).

To confirm the utility of our reaction, we demonstrated the catalytic asymmetric synthesis of the biologically interesting kainic acid analogue **12**, which was originally developed by Hashimoto and Shirahara[13] as a potent glutamate receptor agonist (Scheme 2).[4] With 1 mol % Ni catalyst, the Michael adduct **10** was efficiently synthesized in 93% yield with 91% ee in spite of the possible negative interaction caused by the *o*-MeO group. Upon reduction with Raney Ni, the 2,3,4-cis-substituted pyrrolidine was obtained directly. After N-protection, epimerization of the 2-position occurred under modified basic conditions,[14] affording the 2,3-trans-3,4-cis isomer **11**. Further conventional oxidations followed by deprotection with trifluoroacetic acid (TFA) completed the catalytic asymmetric total synthesis of **12** in 42% overall yield in only eight steps starting from the corresponding α-ketoester.

In summary, we have described the first example of a diastereo- and enantioselective conjugate addition of α-ketoesters to nitroalkenes with broad generality. The reaction was applicable to various substrates and proceeded well in environmentally friendly alcoholic solvent. The combination of endogenous and exogenous bases was effective, allowing a small amount of the catalyst to promote the reaction efficiently. Further investigations of the scope of the reaction and mechanistic studies[11] are underway in our laboratory.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (19028065, "Chemistry of Concerto Catalysis"), Special Project Funding for Basic Science. S.L. is grateful to JSPS for financial support.

Supporting Information Available: Experimental procedures and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) See the Supporting Information for the solvent and ester effects.
(9) $NiBr_2$•(**7**)$_2$, developed by Evans et al. for the asymmetric conjugate addition of malonates to nitroalkenes, was inferior for the present reaction [78%, 59% ee (2 mol % Ni, toluene, 6 h); 78%, 29% ee (2 mol % Ni, 2-propanol, 68 h)] (see: Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583). Additionally, the corresponding $Ni(ClO_4)_2$ complex gave *ent*-**3a** in 40% yield with 40% ee after 48 h.
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JA909457B