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Catalytic Asymmetric α-Chlorination of 3-Acyloxazolidin-2-one with a Trinary Catalytic System

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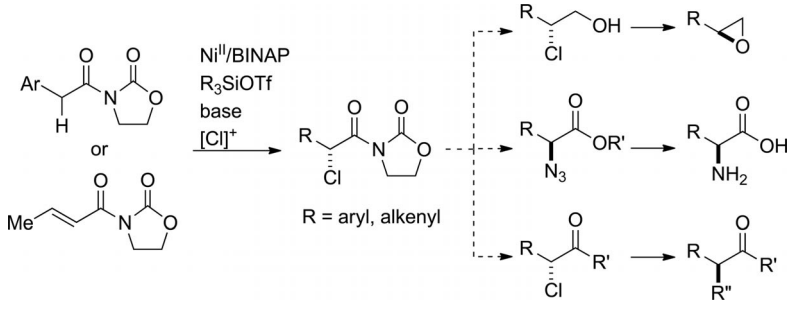
Direct asymmetric α-chlorination of aryl acetic acid derivatives was achieved with a novel trinary activation system consisting of a catalytic amount of $NiCl_2$/(*R*)-BINAP, Et_3Si-OTf, and a tertiary amine base. The reaction smoothly afforded the chlorinated compound in good yield with up to 89 % *ee*. Application of this reaction to a less acidic crotonic acid derivative gave the β,γ-unsaturated α-chlorinated compound through deprotonation at the γ-position.

Introduction

Because the chlorine atom is a good leaving group, substitution reactions of alkyl chlorides with various nucleophiles are routinely employed in organic synthesis. Such reactions occur through S_N2-type displacement with (complete) inversion of the stereochemistry. For this reason, optically active chlorinated compounds can serve as versatile intermediates for further chemical modifications. Asymmetric α-halogenation reactions have progressed substantially in the last decade.[1] One of the great achievements in this field is cinchona alkaloid catalyzed chlorination/bromination of acid chlorides through the formation of ketene intermediates.[2] Another example is chiral secondary amine catalyzed chlorination/bromination of primary aldehydes.[3] In addition to electrophilic halogenation reactions, MacMillan and co-workers reported an oxidative nucleophilic α-chlorination of aldehydes by using LiCl in combination with $Cu(OCOCF_3)_2$/$Na_2S_2O_8$.[4] As for chiral Lewis acid catalyzed reactions, active methine compounds such as α-substituted β-keto esters and 3-substituted oxindole derivatives have been chlorinated with excellent enantioselectivity.[5,6]



Scheme 1. α-Chlorination and potential chemical transformations.

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As a part of our continuing studies on transition metal enolate chemistry[7] and fluorine chemistry,[8] we previously developed a novel trinary catalytic system consisting of $NiCl_2$/(*R*)-BINAP (**1a**), a secondary Lewis acid (R_3SiOTf), and 2,6-lutidine for catalytic asymmetric α-monofluorination of aryl acetic acid derivatives.[9] On the basis of those results, we hypothesized that a similar chlorination reaction would also occur enantioselectively with the trinary catalyst (Scheme 1). In principle, the obtained chlorinated compounds can be converted into various useful compounds.[1,3b] For example, reduction followed by basic treat-

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ment will give optically active terminal epoxides. Simple substitution reaction with sodium azide may give precursors to chiral aryl glycine derivatives. Furthermore, after conversion of the products into the corresponding ketones, the chlorine atom could be substituted by organozinc reagents in the presence of a copper catalyst.[10] Because of their synthetic utility, highly diastereoselective chlorination reactions of chiral 3-acyl oxazoridin-2-ones have been developed.[11] However, the direct catalytic conversion of ester equivalents has rarely been reported.[12] Here, we describe the catalytic asymmetric α-chlorination of aryl acetic acid derivatives by using our trinary activation system. We modified the original conditions and found that tertiary amine bases were more effective than 2,6-lutidine so that not only aryl acetic acid derivatives but also an α,β-unsaturated compound were chlorinated smoothly in an enantioselective manner.

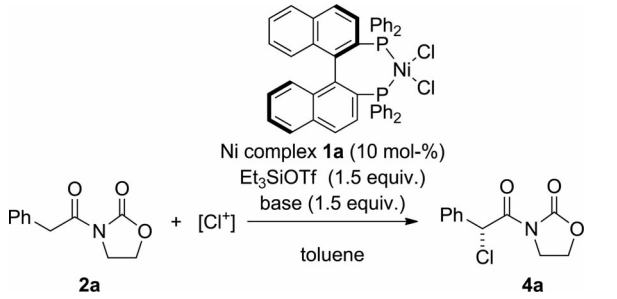
Results and Discussion

Initially, we examined several chlorinating reagents under the optimized conditions for the fluorination reaction[9] (Table 1). For these reactions, we utilized *N*-acyl oxazolidin-2-one (**2a**) as a model substrate, as the corresponding *N*-acyl thiazolidin-2-one, which was examined in our previous study, gave an inseparable mixture of the product and the starting material. Although the reaction with NCS, a commonly used chlorinating reagent, proceeded smoothly, negligible asymmetric induction was observed (Table 1, Entry 1). Interestingly, trifluoromethanesulfonyl chloride (TfCl, **3**) was found to be suitable for use under our reaction conditions,[13,14] and desired product **4a** was obtained with moderate enantioselectivity (Table 1, Entry 2). To accelerate the reaction, Et_3N was tested in place of 2,6-lutidine. As we had hoped, the reaction was accelerated, reaching completion within only 1 h to afford **4a** almost quantitatively with 43%*ee* (Table 1, Entry 3).[15] The reaction temperature and the concentration of the reaction mixture influenced the selectivity (Table 1, Entries 4 and 5).[16] To our delight, when less basic *N*-methylmorpholine (NMM) was used, the *ee* was improved to 87% (Table 1, Entries 6 and 7), and although a lower temperature gave a slightly improved *ee*, the longer reaction time was unfavorable (Table 1, Entry 8).

Obtained product **4a** was hydrolyzed[17] to give corresponding carboxylic acid **5** quantitatively (Scheme 2). Negligible loss of optical purity during the hydrolysis was confirmed after conversion into methyl ester **6**. The absolute configuration of **4a** was determined to be *R* by comparing the retention times of both enantiomers of **6** on a chiral stationary phase with the reported data,[18,19] and this result is in accord with the sense of enantioselection observed in the previous fluorination reaction.[9]

Under the optimized reaction conditions, we next examined the generality of the reaction by using various aryl acetic acid derivatives (Table 2). In most cases, the reaction proceeded smoothly to afford the desired monochlorinated

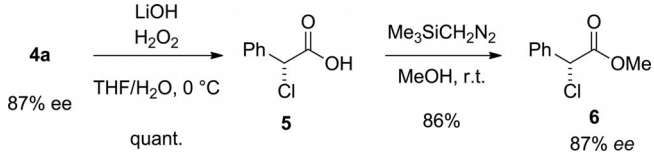
Table 1. Optimization of the reaction conditions.



2a 4a

Entry	Base	[Cl⁺]	*c* [M]	*T* [°C]	*t* [h]	Yield[a] [%]	*ee*[b] [%]
1	2,6-lutidine	NCS	1.0	–20	24	93	<10
2	2,6-lutidine	TfCl (**3**)	1.0	–20	24	77	30
3	Et_3N	**3**	1.0	–20	1	99	43
4	Et_3N	**3**	1.0	–40	1	93	64
5	Et_3N	**3**	0.1	–40	3	96	79
6	NMM	**3**	0.1	–40	1	85	85
7	NMM	**3**	0.1	–60	6	94	87
8	NMM	**3**	0.1	–78	72	81	89

[a] Isolated yield. [b] Determined by chiral HPLC analysis. NMM = *N*-methylmorpholine.



Scheme 2. Hydrolysis of **4a**.

compounds in high yield with up to 88%*ee*. Interestingly, the dichlorinated compound was not isolated in any of these reactions. Ether, thioether, and halogens were tolerant to the present conditions (Table 2, Entries 1–6). Bulkier substrates such as **2h** and **2i** were also chlorinated smoothly (Table 2, Entries 7 and 8). When the amount of the catalyst was reduced to 5 mol-%, similar results were obtained (Table 2, Entry 9). It is advantageous that a stable $NiCl_2$/BINAP complex can be used without the need to prepare the corresponding cationic Ni complex, such as the Ni(OTf)$_2$/BINAP complex, which generally requires the use of expensive silver triflate.

In view of the strong activation ability of the modified trinary system described above, we next examined the reactions of less acidic substrates. No reaction was observed in the case of an aliphatic substrate derived from hexanoic acid. In contrast, γ-deprotonation and α-chlorination of crotonic acid derivative **7** occurred (Scheme 3).[20] Though **7** was recovered under the reaction conditions optimized for **4a**, the reaction proceeded at –40 °C when Et_3N was used in place of NMM. Monochlorinated product **8** was obtained in 62% yield with reasonably high enantioselectivity of 72%.

Because product **4** is likely to be more acidic than the starting material due to the presence of an electron-withdrawing chlorine atom, we first considered that lower

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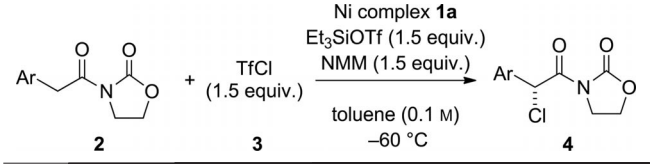
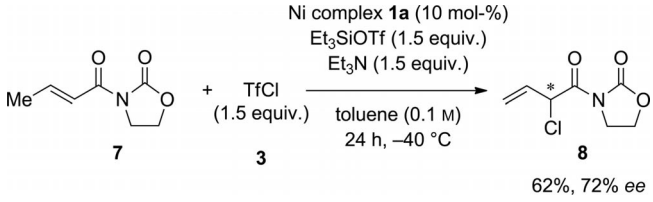
Table 2. Scope of the reaction.



Entry	Substrate	Ar	**1a** [mol-%]	*t* [h]	Yield[a] [%]	*ee*[b] [%]
1	**2b**	*p*-MeC_6H_4	10	24	86	83
2	**2c**	*p*-$MeOC_6H_4$	10	24	86	83
3	**2d**	*m*-$MeOC_6H_4$	10	24	89	80
4	**2e**	*p*-FC_6H_4	10	24	89	86
5	**2f**	*p*-BrC_6H_4	10	6	87	75
6	**2g**	*p*-$MeSC_6H_4$	10	6	93	76
7	**2h**	1-naphthyl	10	24	94	88
8	**2i**	2-naphthyl	10	16	96	78
9	**2a**	Ph	5	12	99	84

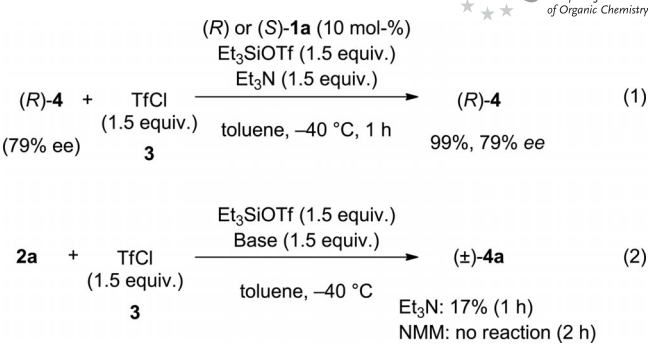
[a] Isolated yield. [b] Determined by chiral HPLC analysis.



Scheme 3. Catalytic asymmetric α-chlorination of crotonyl derivative **8**.

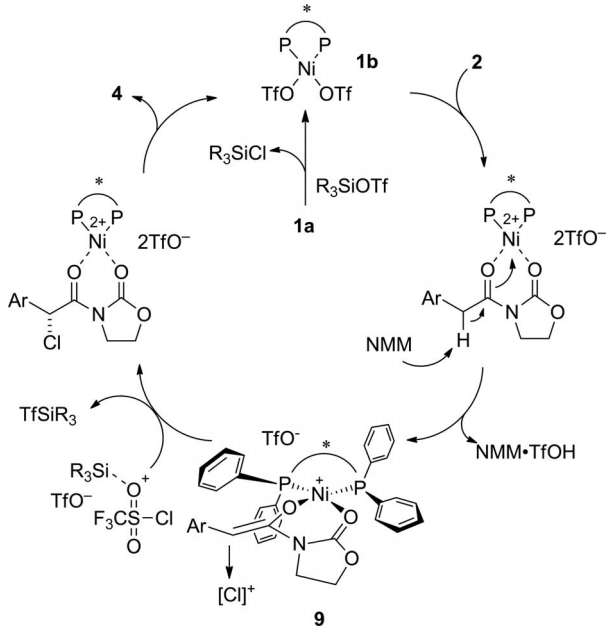
enantioselectivity observed in the case of Et_3N might be associated with in situ racemization of the product. Isolated compound (*R*)-**4a** (79%*ee*) prepared with the $NiCl_2$/(*R*)-BINAP complex was therefore treated under identical conditions with the two enantiomers of the $NiCl_2$/BINAP complex. As shown in Scheme 4, (*R*)-**4a** was recovered quantitatively without any loss of optical purity, which strongly indicates that no racemization of the product occurred in the reaction mixture (Scheme 4, Equation 1). Thus, we suspected that the uncatalyzed reaction might proceed in the presence of the silyl triflate and Et_3N. Control experiments revealed that TESOTf and Et_3N alone could promote the reaction even at –40 °C (Scheme 4, Equation 2). In contrast, the reaction with NMM did not give **4a** at all. These results suggest that the occurrence of uncatalyzed reaction might decrease the enantioselectivity.

The proposed reaction mechanism is outlined in Scheme 5. On the basis of previous NMR spectroscopic experiments, it seems likely that **1a** is converted into active Ni triflate complex **1b** as a result of counteranion exchange with Et_3SiOTf.[9,21] Because the isolated $Ni(OTf)_2$/BINAP complex and Et_3N alone did not promote the reaction, the three activators are considered to act cooperatively to promote the reaction enantioselectively. Imide **2** coordinates to the active Ni species, and Ni enolate **9** with the *Z* configuration would be formed with the aid of the amine base. Even though the exact role of Et_3SiOTf is not clear at present, we speculate that the secondary Lewis acid activates TfCl



Scheme 4. Control experiments.

to enhance its electrophilicity. The absolute configuration observed in this reaction suggests that TfCl attacks the Ni enolate from the *Re* face, which is sterically less hindered.



Scheme 5. Proposed catalytic cycle.

Conclusions

In summary, the modified Ni-based trinary system was found to promote the asymmetric α-chlorination of aryl acetic acid derivatives. Notably, this powerful trinary system allowed in situ activation of α,β-unsaturated compound **7**, and γ-deprotonation followed by α-chlorination occurred enantioselectively. Although further improvement is required, our results demonstrate the great potential of our cooperative activation method.

Experimental Section

Starting imide **4** (0.1 mmol) and Ni complex **1a** (0.01 mmol, 7.5 mg, 10 mol-%) were suspended in toluene (1.0 mL, 0.1 M) under an atmosphere of dry nitrogen. The resulting mixture was sonicated at ambient temperature for 2 min, and a dark purple solution was

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obtained. Then, TESOTf (0.15 mmol, 32 μL) was added at –60 °C, and the mixture was stirred for 10 min at the same temperature. The solution was sonicated at ambient temperature for 2 min, affording a red-brown solution. Trifluoromethanesulfonyl chloride (TfCl, 0.15 mmol, 16 μL) was added at –60 °C. Next, *N*-methylmorpholine (NMM, 0.15 mmol, 20 μL) was added, and the reaction mixture was stirred for the time given in Table 2. The reaction was monitored by TLC (hexane/AcOEt) until completion, and then the mixture was quenched with aqueous NaCl. Usual workup and flash column chromatography were carried out for purification.

Supporting Information (see footnote on the first page of this article): General remarks, procedures, and compound characterization data.

Acknowledgments

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[21] The exact structure of **1b** has not yet been determined.

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