

TCIMAIL

number **144**



CONTENTS

2 Contribution :

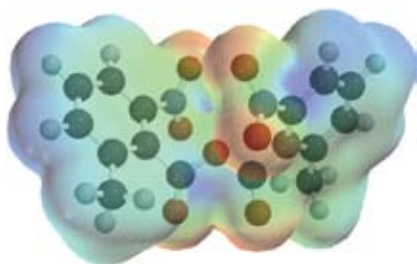
- Various Synthetic Methods Using Aromatic Carboxylic Anhydrides

Isamu Shiina
Professor of Faculty of Science,
Tokyo University of Science

17

New Products Information :

- Useful Chiral Dirhodium(II) Complex Catalyst
- SingaCycle™-E1
Catalyst for the Heck-Mizoroki Reaction
- Highly Effective Iodinating Reagent



MNBA

Contribution

Various Synthetic Methods Using Aromatic Carboxylic Anhydrides

Isamu Shiina

Faculty of Science, Tokyo University of Science
1-3 Kagurazaka, Shinjuku-ku, Tokyo 162-8601

Abstract

As a result of pursuing dehydrating condensation reagents, which can be stably stored at room temperatures, easy to handle, and highly reactive, it was found that aromatic carboxylic anhydrides can be used as versatile highly functional reagents. Reaction by using TFBA or BTFBA with a Lewis acid catalyst can be one of the most powerful protocols for carbon-oxygen bond formation, which enable the synthesis of the desired carboxylic esters and lactones in good yields. Furthermore, the use of MNBA or DMNBA with a nucleophilic catalyst under basic conditions enables convenient preparation of acid-sensitive carboxylic esters, lactones, and amides. In addition, the use of PMBA or benzoic anhydride with an asymmetric catalyst realizes the kinetic resolution of racemic secondary alcohols and racemic 2-arylpropionic acids, resulting in the establishment of a novel synthetic method for optically active carboxylic esters, secondary alcohols, and 2-arylpropionic acids.

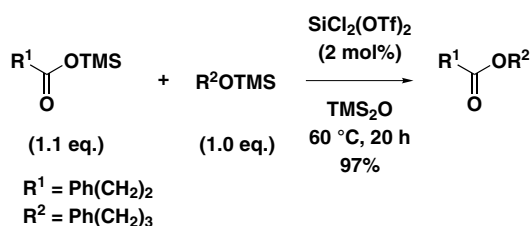
1. Introduction

To synthesize organic substances efficiently in an artificial way, it is required to develop convenient methods for forming (1) carbon-carbon bonds; (2) carbon-hydrogen bonds; (3) carbon-oxygen bonds; and (4) carbon-nitrogen bonds with high selectivities. With a rapid advancement of organic synthesis over the past twenty years, more and more excellent chemical conversion methods have been developed. The establishment of the “acyclic stereocontrolled synthesis”, such as the allylation reaction or the aldol reaction, which forms carbon-carbon bonds with regio- and stereoselectivity, made it possible to build the basic carbon framework of complex organic molecules possessing molecular weights of over 1,000 in recent years.

With regards to carbon-hydrogen bonds formation, owing to progress in asymmetric hydrogenation reactions, etc., optically active molecules with their absolute configurations controlled have been obtained. However, compared to the remarkable advances in the studies of (1) and (2), there has been no significant progress until now in the development of novel reactions forming (3) and (4). Under these situations, we tried to discover a series of efficient novel carbon-hetero element bonds forming reactions by using “aromatic carboxylic anhydrides” as condensation reagents. Since these reactions proceed under mild conditions without using harmful substances, such as heavy-metal salts, they are flexible methods for the synthesis of molecules with less environmental burden and can form the carbon-hetero element bond at any desired position with high selectivity. In the present article, we introduce a series of our research results, which have been performed over the past several years covering the range from development to the applications.

2. Discovery of the condensation reaction using “aromatic carboxylic anhydrides”

While researching the chemistry of silyl enol ethers, we studied on silyl esters of carboxylic acids and focused on their effectiveness as acylating reagents. First, we discovered a novel reaction, wherein, in the presence of a Lewis acid catalyst, a nucleophilic substitution reaction occurs between carboxylic silyl esters (electrophile) and an alkyl silyl ether (nucleophile) to afford the corresponding carboxylic ester in high yield (Scheme 1).¹ However, this reaction is a direct transesterification of a carboxylic silyl ester to a carboxylic ester required heat with a process of transformation of a siloxy group to an alkoxy group.



Scheme 1

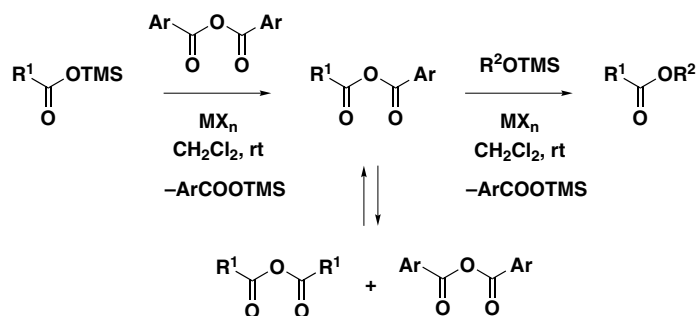
At this stage, we decided to reinvestigate an alternative method for the preparation of carboxylic esters using different reagents under milder conditions.

Acetyl chloride and benzoyl chloride, for example, are frequently used for the acylation of alcohol, and acetic anhydride is also used as a reagent suitable for acetylation. On the other hand, aromatic carboxylic anhydrides have especially poor reactivity, therefore, they are rarely used for the direct benzylation of alcohol. Thus, we assumed that with the less reactive property of benzoic anhydride as an acyl donor, the corresponding aliphatic carboxylic esters can be selectively obtained from aliphatic carboxylic silyl esters and alkyl silyl ethers (Scheme 2).

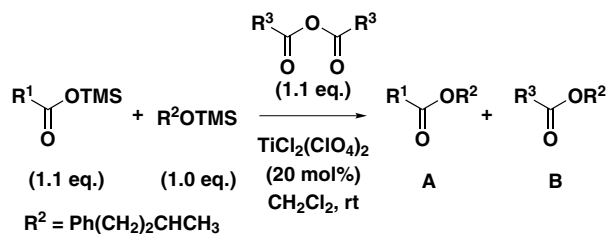
First, an acyl transfer reaction proceeds smoothly between aliphatic carboxylic silyl esters and aromatic carboxylic anhydrides. Next, part of the mixed anhydride generated rapidly disproportionates into two kinds of symmetrical acid anhydrides, therefore, three kinds of acid anhydrides in total must be rapidly put in the equilibrium mixture state in the reaction system. Since the reactivity of acid anhydrides in general becomes higher in the order of symmetrical aromatic carboxylic anhydride < symmetrical aliphatic carboxylic anhydride < mixed anhydride, it is assumed that the most reactive mixed anhydride will react preferentially with a nucleophile. Furthermore, if the reactivity of the aliphatic carboxylic acid moiety in the mixed anhydride is higher than that of the aromatic carboxylic acid moiety, an alkyl

silyl ether must attack preferentially the aliphatic acyl moiety to afford the corresponding aliphatic carboxylic ester along with the elimination of aromatic carboxylic silyl ester.

In fact, when trimethylsilyl ether of 4-phenyl-2-butanol was added to a mixed anhydride prepared in advance from acetic acid trimethylsilyl ester and benzoic anhydride by using $\text{TiCl}_2(\text{ClO}_4)_2$ as a Lewis acid catalyst, the desired ester **A** was obtained in 90% yield, along with the undesired ester **B** (1%) generated by the direct reaction of benzoic anhydride and the trimethylsilyl ether (Table 1, Entry 1). The result revealed that in the first stage of the reaction, conversion to mixed anhydride from benzoic anhydride proceeded smoothly, and the formation rate of benzoic ester was much slower than that of aliphatic acid ester. When the same experimental procedure using other anhydrides available was carried out, interesting results were obtained as described in Entries 2–4. Though pivalic anhydride or trifluoroacetic anhydride are useful reagents for preparing mixed anhydrides in peptide synthesis, they are not suitable for this condensation reaction. For example, in the reaction using the anhydrides, a considerable amount of the undesired esters **B** (pivalic ester or trifluoroacetic ester) is unexpectedly generated as a byproduct (Entries 2 and 3). On the other hand, as Entry 4 shows, the transesterification of pivalic acid trimethylsilyl ester using benzoic anhydride afforded **A** in excellent yield, which revealed that aliphatic acid esters are in general formed preferentially over benzoic esters under the conditions.



Scheme 2



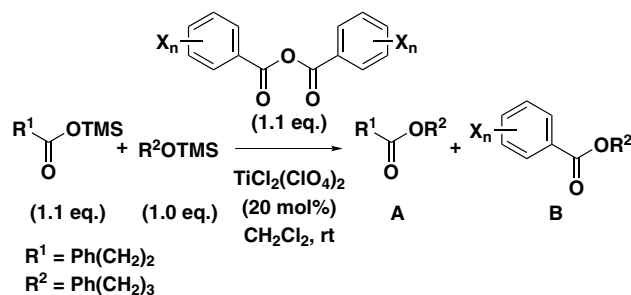
Entry	R ¹	R ³	Yield of A / %	Yield of B / %
1	Me	Ph	90	1
2	Me	^t Bu	30	47
3	Me	CF ₃	39	23
4	^t Bu	Ph	89	4

Table 1

3. Esterification reaction using 4-trifluoromethyl benzoic anhydride (TFBA)²

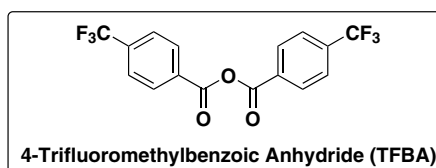
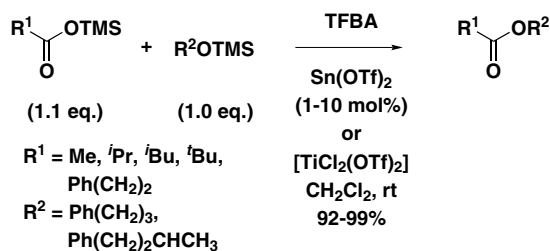
In order to develop synthetic methods applicable to intramolecular condensation, it is required to design synthetic protocols giving the target products in high yields from nearly equimolar amounts of two starting materials. Furthermore, for the purpose of enhancing the yields of cyclized products, it is essential to develop a novel synthetic method for esters with perfect chemoselectivity. Thus, we tried to increase both the yield and chemoselectivity by introducing various substituents on aromatic rings in the dehydrating condensation reagents (Table 2). For example, comparing Entry 1 with Entries 4–6 shows that the introduction of an electron-withdrawing group to the 4-position of the aromatic ring

enhances the chemoselectivity. In particular, the reaction using 4-trifluoromethylbenzoic anhydride (TFBA) afforded almost perfect selectivity of the desired aliphatic carboxylic ester with no generation of benzoic ester by NMR detection. Furthermore, as Entries 2 and 3 show, the introduction of chlorine to the 2-position of the aromatic ring produced the same or a little less selectivity. On the other hand, in the case of using substituted benzoic anhydrides possessing a methoxy or a methyl group, the selectivities were reversed, affording preferentially the undesired benzoic esters over the desired aliphatic carboxylic esters (Entries 7–10). From these results, it was found that the introduction of a strong electron-withdrawing group to the 4-position of an aromatic ring was effective; in particular, TFBA with a trifluoromethyl group functioned best as a condensation reagent.



Entry	X _n	Yield / %	A / B
1	H	98	16 / 1
2	2-Cl	89	13 / 1
3	2,6-Cl ₂	68	3.5 / 1
4	4-Cl	60	32 / 1
5	4-F	93	49 / 1
6	4-CF ₃	91	>200 / 1
7	4-MeO	95	1 / 1.6
8	2-MeO	91	1 / 24
9	2-Me	90	1 / 1.8
10	2,6-Me ₂	97	1 / 32

Table 2



Scheme 3

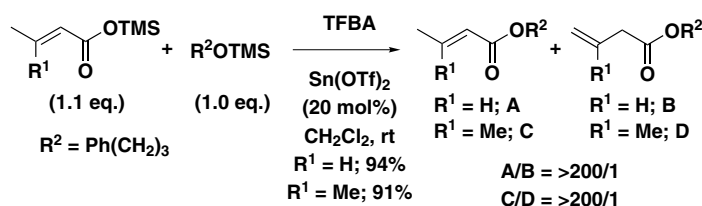
Next, we examined the versatility of this esterification promoted by Lewis acids, such as $\text{Sn}(\text{OTf})_2$ and $\text{TiCl}_2(\text{OTf})_2$. As a result, it was found that isobutyric acid, isovaleric acid, pivalic acid, and 3-phenylpropionic acid trimethylsilyl esters rapidly react with alkyl trimethylsilyl esters to afford the corresponding carboxylic esters almost quantitatively (Scheme 3). Furthermore, in the presence of TFBA, the esterification proceeded to afford the target compounds in 90% or more yield even with less than 1 mol% of a Lewis acid.

The synthesis of high-purity conjugated carboxylic esters could be achieved as an application example of the esterification method. α,β -Unsaturated esters, such as crotonic acid, senecioic acid and angelic acid ester, carry a fear of isomerization under basic conditions, which causes the troublesome generation of side products. In contrast, only the target products can be selectively obtained in esterification by using TFBA (Scheme 4).^{2b}

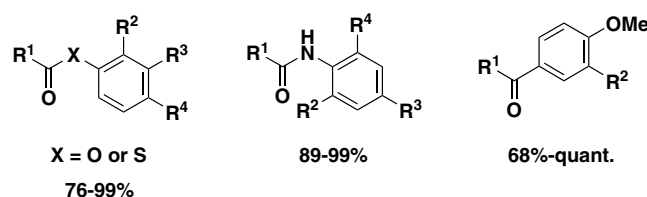
Furthermore, it is noted that TFBA is also effective for the synthesis of active esters, such as nitrophenol esters and benzenethiol esters,^{2b,3} substituted anilides,⁴ and aromatic ketones⁵ (Scheme 5). In addition, this method is also effective for introducing a formyl group to indole rings as well as traditional methods such as the Gattermann–Koch reaction or the Vilsmeier reaction. Thus, we succeeded in developing an effective method for preparing 3-formylindole directly from formic acid (Scheme 6).⁶

4. Lactonization reaction of silyl esters of ω -siloxy-carboxylic acids using TFBA⁷

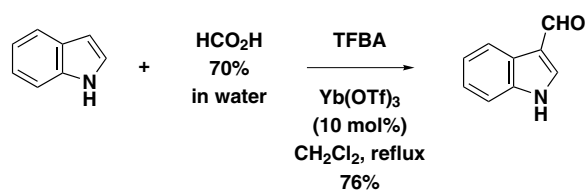
It is unexpectedly difficult to apply a condensation method into intra-molecular reactions. In fact, although more and more new synthetic methods have been reported, there are only few reports on effective lactone synthesis so far. This is attributed to the difficulties in the reaction design which can enhance intra-molecular reactions under low substrate concentrations as well as the development of novel reagents which can activate either a carboxyl group or hydroxyl group selectively. The effective methods for solving these problems to enable the synthesis of natural products are as follows: (1) the Mukaiyama–Corey method (*S*-pyridylester method); (2) the Mukaiyama method (onium salt method); (3) the Masamune method (thiol ester activation method); (4) the Yamaguchi method (2,4,6-trichlorobenzoyl chloride/ Et_3N /DMAP method); and (5) the Steglich–Keck method (DCC/DMAP-HCl method). However, all methods must be performed in general at high temperatures under high-dilution conditions so that the intra-molecular reaction proceeds much preferentially over the inter-molecular reaction. Under such conditions, reactions using unstable substrates sometimes afford the desired cyclized products in poor yields. We attempted lactonization of the silyl derivative of ω -hydroxycarboxylic acid with the expectation that the carboxyl moiety would be selectively activated by the treatment with TFBA, resulting in rapid ring closing of the



Scheme 4



Scheme 5



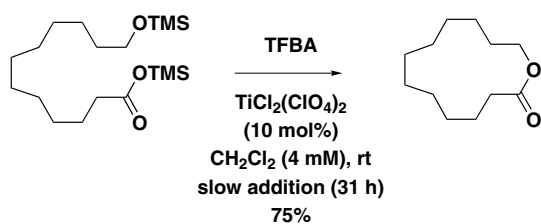
Scheme 6

generated mixed anhydride. As a result, the chemoselective activation was fortunately achieved, which revealed that the mixed anhydride initially generated from silyl ester of ω -siloxy-carboxylic acid and TFBA was rapidly cyclized to afford the corresponding large-sized lactones (Scheme 7). This method makes it possible to prepare 13-membered or more large-sized lactones, accompanying a very little amount of the corresponding 26-membered or large-sized dilactones. Furthermore, the activities of the Lewis acid catalysts were enhanced in the order of $\text{Sn}(\text{OTf})_2 < \text{TiCl}_2(\text{SbF}_6)_2 < \text{TiCl}_2(\text{OTf})_2 < \text{TiCl}_2(\text{ClO}_4)_2$.

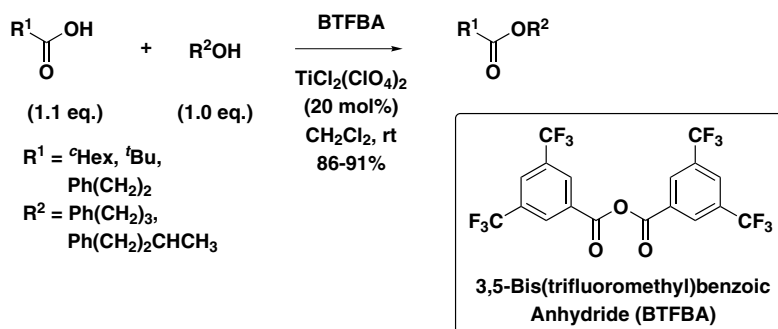
5. Condensation reaction of free carboxylic acids and alcohols by using TFBA and its analogs⁸

In the aforementioned reaction, it was required to prepare silyl derivatives in advance from carboxylic acids and alcohols. In order to develop a more convenient method, we screened various aromatic carboxylic anhydrides as effective dehydrating reagents. Although at first, there was a problem that some catalysts were deactivated during the reactions proceeded, resulting in deteriorated yields, we finally obtained the desired carboxylic esters in excellent yields by using 3,5-bis(trifluoromethyl)benzoic anhydride (BTFBA) possessing stronger electron-withdrawing rings than TFBA (Scheme 8).

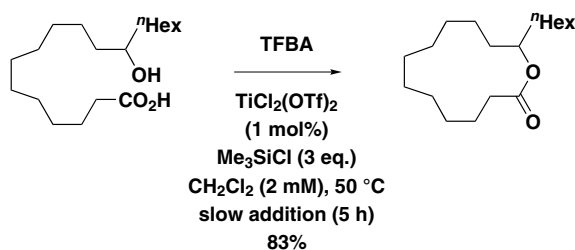
Furthermore, the intra-molecular dehydration condensation of a free hydroxycarboxylic acid by using 3 equivalents of trimethylchlorosilane afforded the desired macrolactone in good yield similar to that obtained by the silyl ester method.^{8b,9} Under the optimized reaction conditions, commercially available TFBA can be used for the lactonization instead of BTFBA. In particular, the cyclization reaction of 12-hydroxystearic acid proceeds smoothly even with 1 mol% of Lewis acid to afford the corresponding 13-membered lactone in 83% yield (Scheme 9).



Scheme 7



Scheme 8

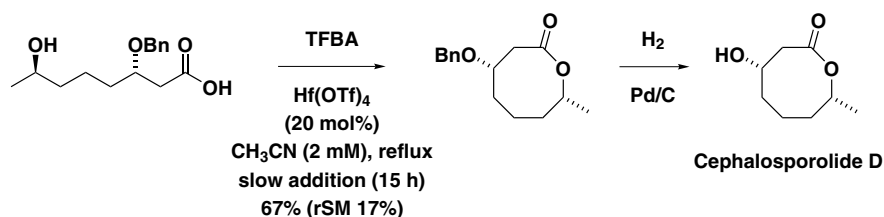


Scheme 9

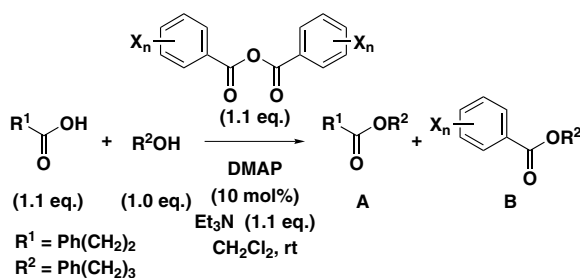
In addition, the macrolactonization reaction by using the Group 4 metal triflate, $\text{Hf}(\text{OTf})_4$ as the Lewis acid proceeded smoothly in the presence of TFBA to afford the corresponding lactones. Furthermore, it is notable that even medium-sized ring molecules can be obtained with this method. For example, the synthesis of the 8-membered lactone moiety of Cephalosporolide D was successfully achieved by applying this method (Scheme 10).¹⁰

6. Esterication by using 2-methyl-6-nitrobenzoic anhydride (MNBA)¹¹

The aforementioned “substituted benzoic anhydride method” is effective for the preparation of molecules possessing acid-resistant groups, however, there are still many structural restrictions in synthesizing polyfunctional natural products. Therefore, we conducted closer screening on novel aromatic carboxylic anhydrides, which can be activated by a nucleophilic catalyst such as DMAP under basic conditions (Table 3). As shown in Entry 1, the reaction using benzoic anhydride possessing no substituent afforded the target aliphatic carboxylic ester in moderate yield with preferable chemoselectivity ($A/B = 100/1$). Furthermore, when a methoxy group is introduced to the 4-position of the aromatic ring, the chemoselectivity was improved, however, the yield of the target ester **A** decreased due to the inhibition of the reaction (Entry 2). Furthermore, as shown in Entries 3 and 4, by using substituted benzoic anhydrides with electron-withdrawing groups at the 4-position of the aromatic rings, such as TFBA, the reaction rates improved significantly, however the undesired substituted benzoic esters **B** were also generated in 2–4% yields.



Scheme 10

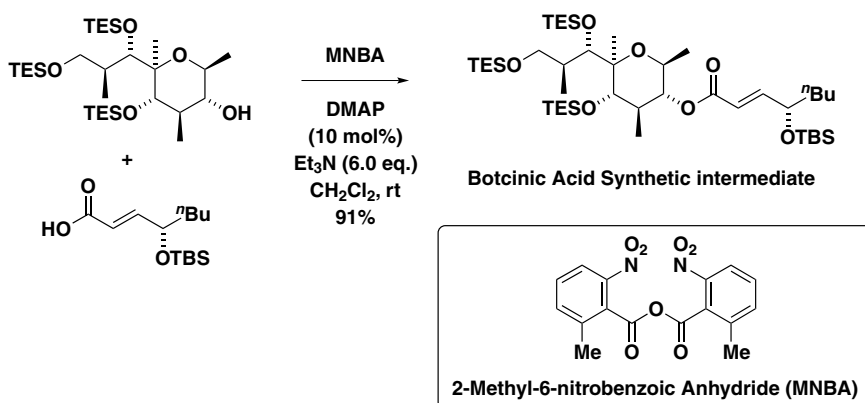


Entry	X	Time / h	Yield / %	A / B
1	H	8	69	100 / 1
2	4-MeO	20	62	170 / 1
3	4-NO ₂	1	74	13 / 1
4	4-CF ₃	1	70	19 / 1
5	2-Me	24	85	100 / 1
6	2,4,6-Me ₃	70	56	>200 / 1
7	2,6-(MeO) ₂	18	82	>200 / 1
8	2,6-Cl ₂	1	72	30 / 1
9	2,4,6-Cl ₃	1	77	27 / 1
10	2-Me-6-NO ₂	1	67	>200 / 1

Table 3

Taking these results into account, we conducted further examinations on the substituent effect at the 2-position on the aromatic rings, expecting the steric interference around the carbonyl group to improve the chemoselectivities. In Entries 5–7, we attempted the synthesis of carboxylic esters by using substituted benzoic anhydrides possessing electron-donating groups, such as a methyl group or a methoxy group, at the 2-position or both the 2- and 6-positions. These reactions showed favorable chemoselectivities on the whole, reducing the yield of the side product **B** to 1% yield or less. However, due to the decreased reactivities, this condition turned out to be still insufficient for lactonization. Furthermore, as shown in Entries 8 and 9, in the reactions using aromatic anhydrides possessing chlorines at both the 2- and 6-positions, the generation of the mixed anhydrides and esterification proceed smoothly, however, the chemoselectivities were not improved compared with that obtained by using TFBA. These results revealed that it is important for a higher reaction rate that the aromatic rings of anhydrides have electron-withdrawing groups, and on the other hand, high chemoselectivity appears when the electron-donating group is introduced to 2-position of the aromatic rings. Based on the consideration of these tendencies, we devised 2-methyl-6-nitrobenzoic anhydride (MNBA), expecting that by using it, both reactivity and chemoselectivity will be improved enough to be applied to intra-molecular reactions. When we used MNBA, which was prepared from 2-methyl-6-nitrobenzoic acid, in the previous model reaction, it was found that the desired condensation reaction proceeded rapidly with no generation of the side product, 2-methyl-6-nitrobenzoic ester (Entry 10).

We have been continuously investigating the synthesis of natural products, applying the MNBA method into inter- and intra-molecular condensation reactions using various substrates. In many cases, desired compounds can be obtained in much higher yields than other existing synthetic methods, which verifies the substrate generality of our method. As shown below, the total synthesis of antibacterial Botcinic Acid was successfully achieved by using MNBA (Scheme 11).¹²



Scheme 11

7. Lactonization reaction using MNBA and its analogue^{11b,13}

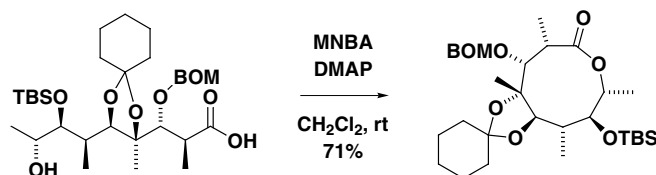
Since we found the optimized conditions for efficient inter-molecular condensation by using MNBA, we also applied this methodology to intra-molecular condensations. The experimental procedure only requires a slow addition of a solution of ω -hydroxycarboxylic acid to a solution (methylene chloride or toluene as solvent) of MNBA and DMAP at room temperature with a syringe pump. Under these reaction conditions, the generation of the mixed anhydride (MA) proceeds continuously and gradually to produce the corresponding lactone. Therefore, the concentration of MA is always low in the solution during the reaction, which produces a highly-diluted condition enhancing the monomer selectivity. Moreover, the activation of MA can be achieved at room temperature, instead of under reflux conditions, which gives a simpler procedure and prevents the degradation of substrates by the nucleophilic catalysts. It is noted that we succeeded in the synthesis of the 9-membered lactone moiety of 2-Epibotcinolide, the first presumed compound of Botcinin E by applying the MNBA method (Scheme 12).¹⁴

When the MNBA method was used for the preparation of the aglycon of Erythromycin A, the desired 14-membered lactone was obtained in quantitative yield.¹⁵ According to the previous reports on the synthesis of aglycons of Erythromycin A, it is known that the efficiency of cyclization differs with combinations of protecting groups introduced to the seco acid, a precursor. As shown in Scheme 13, the lactonization of the seco acid, which has a configuration suitable for ring closing, rapidly proceeds at room temperature to produce quantitatively the aglycon moiety of Erythromycin A within a short time. It is noteworthy that even 20 mol% of DMAP, an activator, is sufficient for the lactonization. The cyclization reaction of the starting material possessing a structure similar to the seco acid, which has been believed not to afford the desired lactone, however, the lactonization using MNBA under heating conditions yielded satisfactory amount of the desired lactone.

This method is applicable to the synthesis of more large-sized lactones. For example, a seco-acid was successfully converted into the corresponding 25-membered α -oxylactone. This intermediate lactone was finally deprotected to afford 2-hydroxytetracosanolide, a defensive salivary secretion of soldier termites (Scheme 15).¹⁶

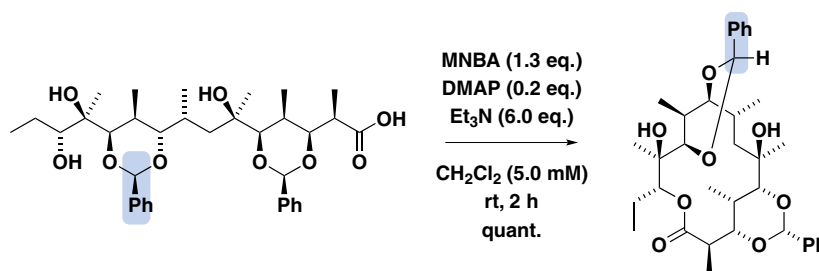
Furthermore, after screening aromatic carboxylic anhydrides possessing a variety of electron-withdrawing groups, it was found that by using 2,6-dimethyl-4-nitrobenzoic anhydride (DMNBA), which has methyl groups at the 2- and 6-positions and a strong electron-withdrawing group at the 4-position, the corresponding carboxylic esters and lactones can be obtained in good yields nearly equivalent to those obtained

using MNBA. Since the reactions by using MNBA and DMNBA generally proceed under mild conditions, successful cyclization of seco acid possessing multiple hydroxyl groups tends to be attained with regioselectivity. As shown below, synthetic musk compound, (9*E*)-Isoambrettolide was successfully obtained in 66% yield in three steps, starting from non-protected Aleuritic Acid (Scheme 16).¹⁷



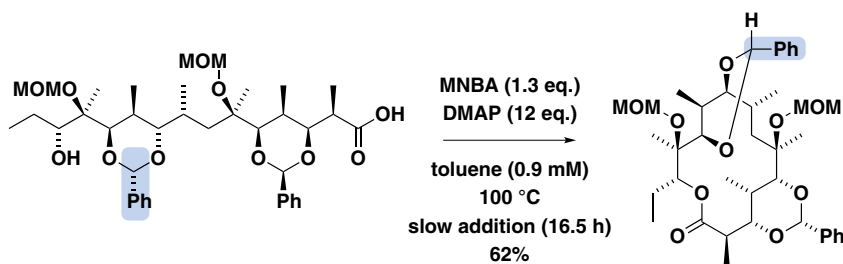
2-Epibotcinolide Synthetic intermediate

Scheme 12



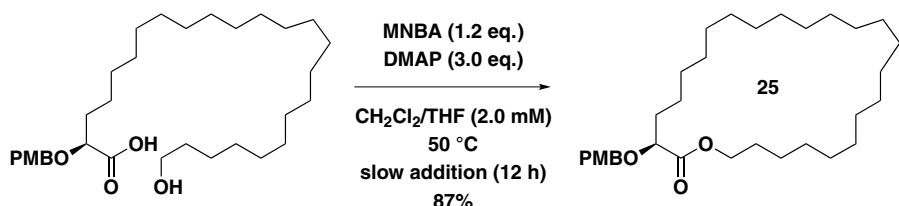
Aglycon of Erythromycin A

Scheme 13



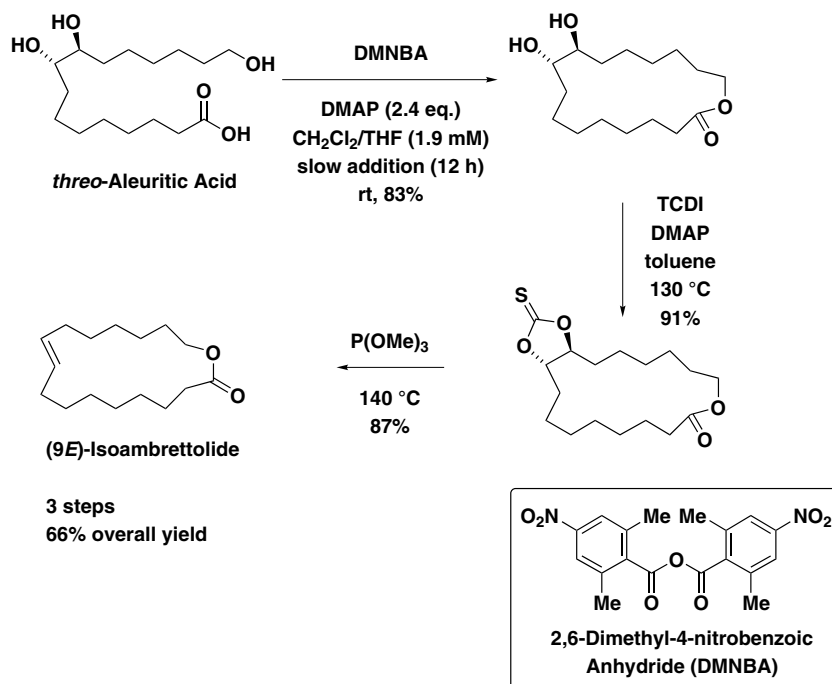
Aglycon of Erythromycin A

Scheme 14



Natural Lactone Synthetic intermediate

Scheme 15



Scheme 16

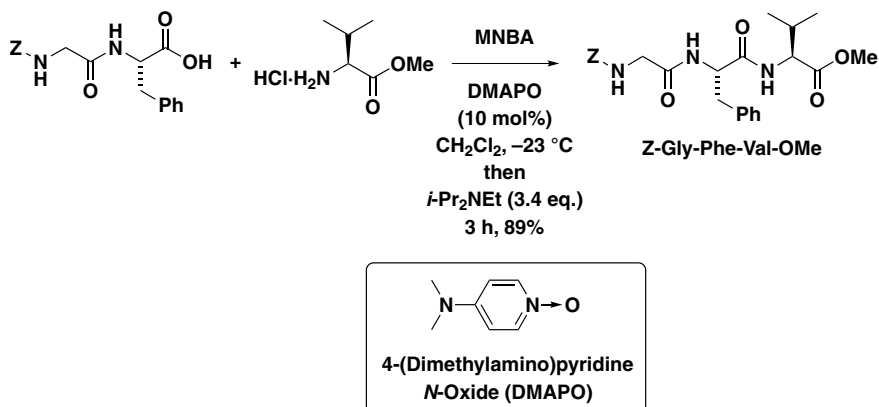
8. Development of pyridine *N*-oxide catalyst DMAPO possessing activity superior to DMAP

The combination of MNBA and DMAP makes it possible to synthesize carboxylic amides from carboxylic acids and amines. However, the application of this method to peptide coupling can not be practical due to potential racemization. After screening suitable nucleophilic catalysts alternating with DMAP under basic conditions, it was found that 4-dimethylaminopyridine *N*-oxide (DMAPO), which has been used in the synthesis of organophosphates, could be applied effectively for peptide coupling. For example, the reaction of *Z*-Gly-Phe with Val-OMe affords the corresponding peptide without racemization (Scheme 17).¹⁸

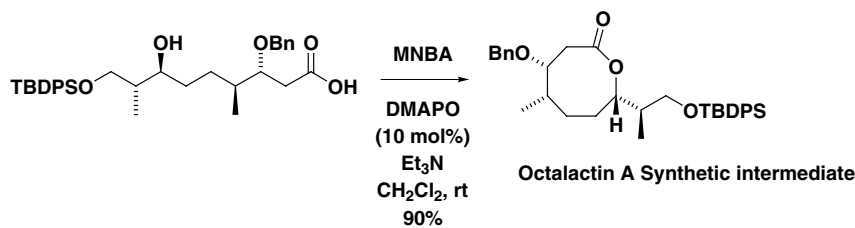
From these results, it was found that DMAPO is an excellent catalyst for lactonization by using aromatic carboxylic anhydrides as condensation reagents. As shown below, in the total synthesis

of Octalactin A, an antineoplastic marine lactone, a catalytic amount of DMAPO (2–10 mol%) functioned efficiently for the formation of the 8-membered ring moiety to afford the desired intermediate in up to 90% yield (Scheme 18).¹⁹

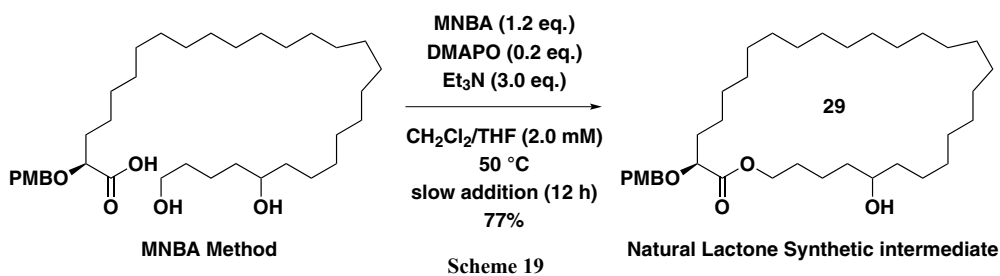
The MNBA/DMAPO method was also successfully introduced into the formation of large-size macrolactones (Scheme 19).^{13b,16,20} As shown below, the total synthesis of the defensive salivary secretion of termites was successfully achieved by combining MNBA and DMAPO, affording the corresponding monohydroxylactone in good yield with perfect regioselectivity. In general, it is known that seco acid, which has a less substituted long chain, tends to have a stable linear conformation, which prevents the lactone formation. Therefore, it is noteworthy that by using our method, the desired macrolactone was successfully obtained in excellent yield (77%). On the other hand, when we compared the result with that obtained by using the Yamaguchi method, the latter yield was only 29% (Scheme 20).



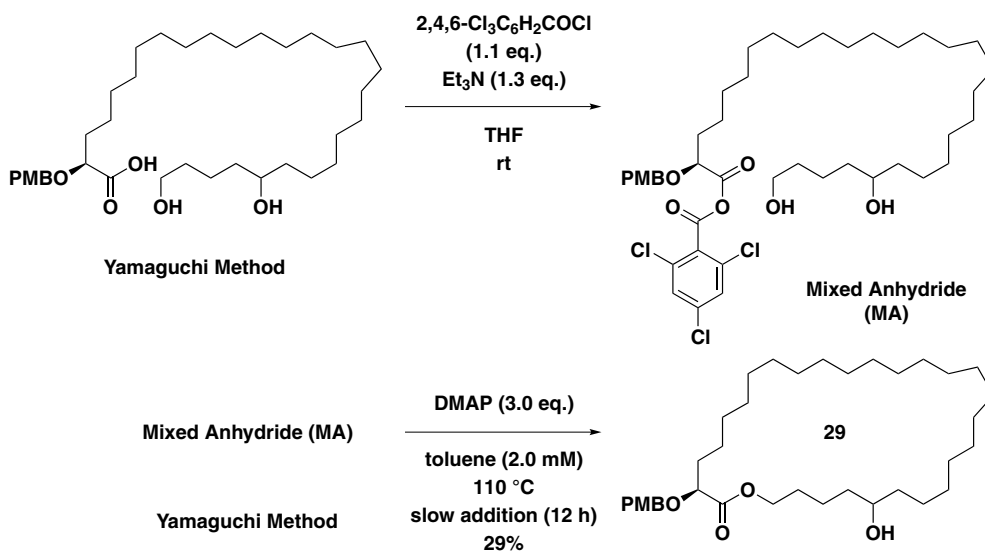
Scheme 17



Scheme 18



Scheme 19



Scheme 20

9. Development of asymmetric esterification using aromatic carboxylic anhydrides as condensation reagents²¹⁻²³

In the previous sections, achiral nucleophilic catalysts were used as promoters. Taking into consideration further application to asymmetric synthesis, we decided to screen chiral nucleophilic catalysts alternating with DMAP. (+)-Benzotetramisole [(*R*)-BTM]²⁴ popularized recently by Birman *et al.* turned out to be an excellent asymmetric catalyst which meets our purpose. By combining it with our dehydrating coupling method, the enantioselective esterification can be achieved. In fact, in the presence of 4-methoxybenzoic anhydride (PMBA) or benzoic anhydride, the reaction of a

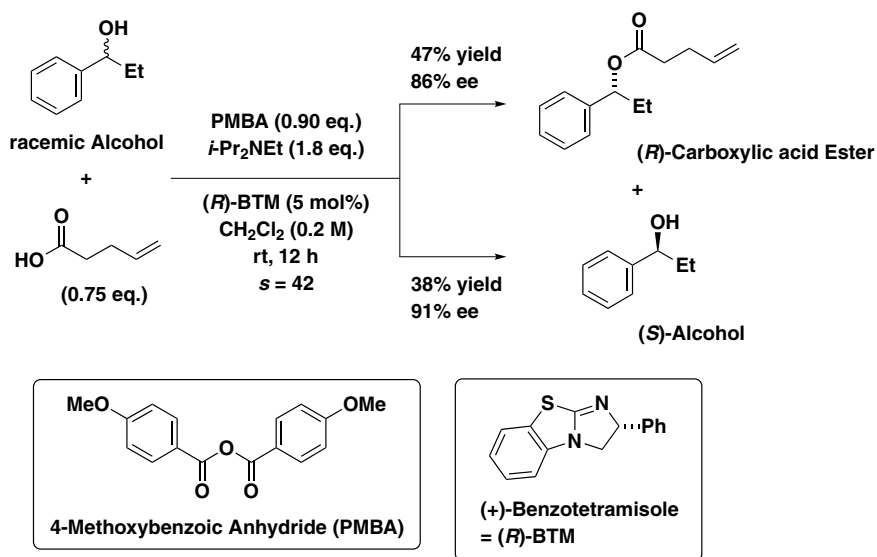
racemic secondary benzylic alcohol with an achiral carboxylic acid afforded the corresponding (*R*)-carboxylic ester and (*S*)-secondary alcohol with excellent enantiomeric excesses (Scheme 21).²¹

The kinetic resolutions of 1-(α -naphthyl)-1-ethanol and 1-(β -naphthyl)-1-ethanol with (*R*)-BTM and benzoic anhydride were successfully carried out with excellent *s*-values, 55 and 43, respectively (Scheme 22). Here, the *s*-value is a factor representing the reaction rate ratio between two enantiomers. In general, if the *s*-value is more than 20, the kinetic resolution can be practically useful. For example, in the reaction of racemic 1-(α -naphthyl)-1-ethanol, the (*R*)-ester was successfully obtained in 50% yield (90% ee). Furthermore, the remaining (*S*)-alcohol could be also recovered in 47% yield (89% ee).

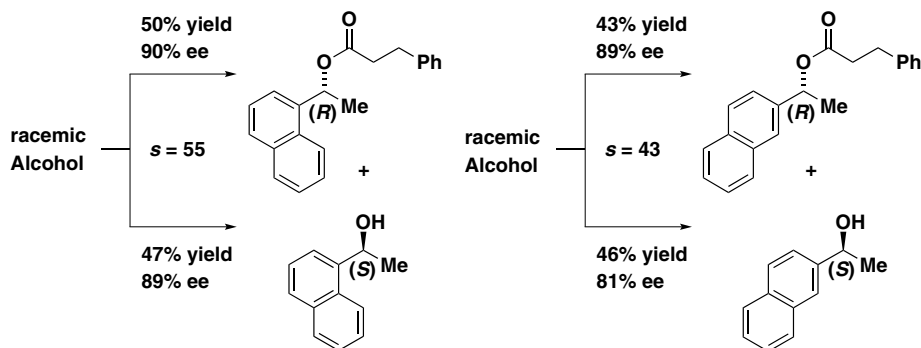
By this novel asymmetrical catalysis, it can be possible to establish a new method for the kinetic resolution of racemic carboxylic acids. After screening achiral alcohols suitable for this purpose, bis(α -naphthyl)methanol was found to be the most effective nucleophile. In fact, when the reaction of racemic 2-arylpropionic acid with bis(α -naphthyl)methanol in

the presence of PMBA or benzoic anhydride was carried out, the asymmetric dehydration reaction proceeded smoothly to afford the target (*R*)-carboxylic ester in high yield with high enantiopurity, along with the remaining (*S*)-2-phenylpropionic acid with moderate enantioselectivity (Scheme 23).²²

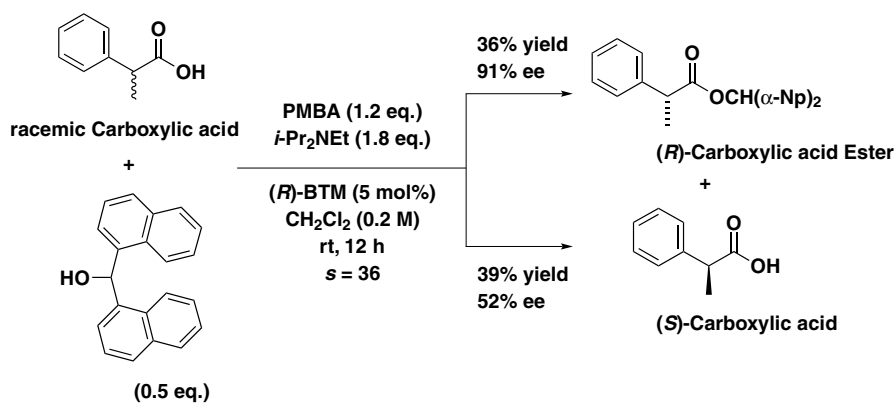
The compounds possessing the 2-arylpropionic acid



Scheme 21



Scheme 22

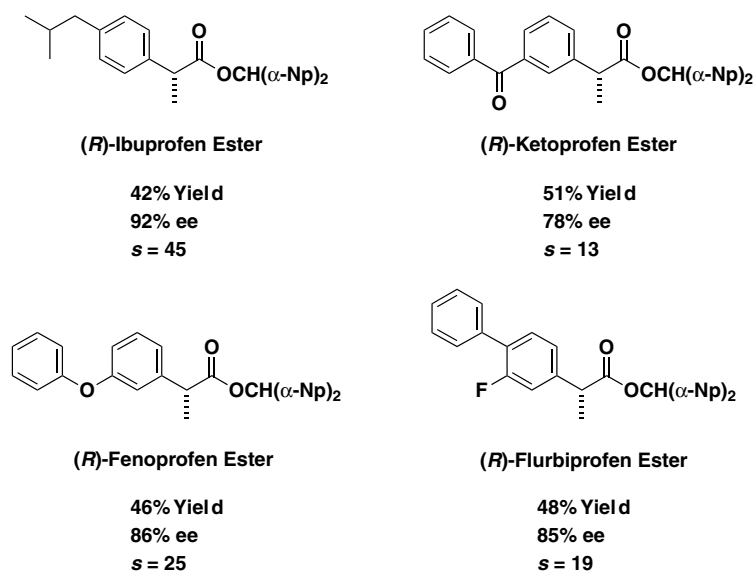


Scheme 23

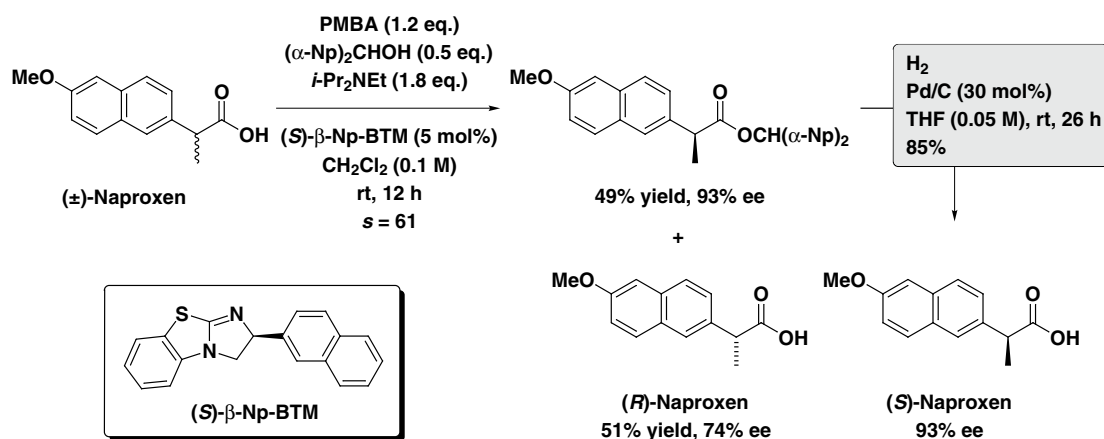
moiety as a basic structure are widely used as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). We also succeeded in establishing a new synthetic method which provides optically active NSAIDs and the ester derivatives in high selectivities (Scheme 24).²² In addition, the resulting bis(α -naphthyl)methyl ester group is easily cleaved under conventional hydrogenation conditions without any loss of optical purity. Therefore, the obtained chiral carboxylic esters can be regarded as suitable precursors of the free carboxylic acids.

Furthermore, we succeeded in the development of (*S*)- β -Np-BTM, a novel nucleophilic catalyst, optimized for the kinetic resolution of racemic α -arylpropionic acids. The use of (*S*)- β -Np-BTM enabled the effective kinetic resolution of racemic naproxen, which finally led to (*S*)-naproxen, an anti-inflammatory substance with high optical purity (Scheme 25).²²

The plausible reaction pathway for the kinetic resolution of racemic carboxylic acids can be illustrated as follows (Scheme 26): The transesterification between benzoic anhydride and racemic carboxylic acids rapidly proceeds in the presence of a nucleophilic catalyst under basic conditions to produce the racemic mixed anhydride (MA), a key intermediate, which is temporarily formed. Among the two enantiomers, the mixed anhydride [(*R*)-MA] generated from the (*R*)-carboxylic acid is preferentially activated by (*R*)-BTM, and then it reacts with bis(α -naphthyl)methanol to afford the corresponding (*R*)-carboxylic acid ester selectively. On the other hand, the mixed anhydride [(*S*)-MA] generated from the (*S*)-carboxylic acid remains unreacted, and is eventually hydrolyzed to afford the (*S*)-carboxylic acid. To support the predicted mechanism above, we determined the preferable two transition states



Scheme 24



Scheme 25

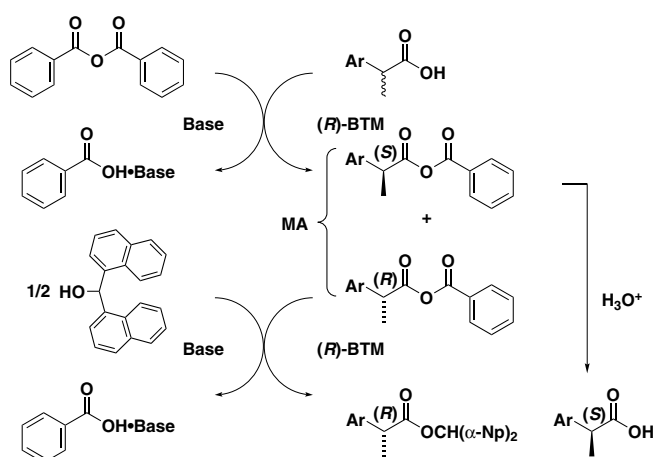
(*R*)-ts and (*S*)-ts, which were derived from (*R*)- and (*S*)-carboxylic acids, respectively, by using the density functional theory (DFT) calculations at the B3LYP/6-31G**/B3LYP/6-31G* level. The comparison of the energies of these transition states revealed that the energy of (*R*)-ts is lower than that of (*S*)-ts. As illustrated in Scheme 27, due to the steric repulsion between the methyl substituent at the α -position of (*S*)-ts and the phenyl group at the C-2 position of the BTM moiety, the stability of (*S*)-ts decreases and the desired (*R*)-carboxylic ester is selectively obtained. Thus, we have disclosed the reaction mechanism and the origin of the enantio-discrimination in the asymmetric condensation reaction by using computational chemistry.

10. Conclusion

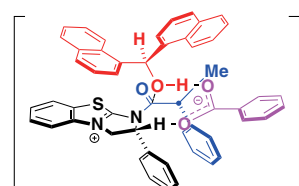
In summary, we outlined briefly the development of the dehydration condensation reactions which have been studied in our laboratory. It is clarified that aromatic carboxylic anhydride, which is a stable and easy-to-handle compound at room temperature, functions as a highly reactive coupling reagent

in combined use with an adequate catalyst. The combination of acidic catalysts with TFBA or BTFBA, or the combination of nucleophilic catalysts with MNBA or DMNBA under basic conditions is suitable for the formation of carboxylic esters and lactones. Both TFBA and MNBA are commercially available, we encourage you to try them. On the other hand, DMAPO, a novel catalyst also functions effectively. DMAPO is also commercially available as a hydrate form, and can be used after a dehydration procedure such as sublimation. The catalytic ability of DMAPO is higher than that of DMAP, and it is noteworthy that by using DMAPO, various peptides can be prepared without significant racemization. Furthermore, in the asymmetric coupling of free carboxylic acids and alcohols, PMBA or benzoic anhydride functions as an effective dehydrating condensation reagent.²³ The combined use of them with an asymmetric catalyst (*R*)-BTM or (*S*)- β -Np-BTM made it easy to obtain a variety of optically active esters, carboxylic acids, and alcohols.

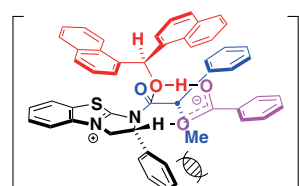
Finally, we would appreciate it if many researchers could use and evaluate the methodologies, and we hope that our research results will be helpful in the progress of synthetic organic chemistry.



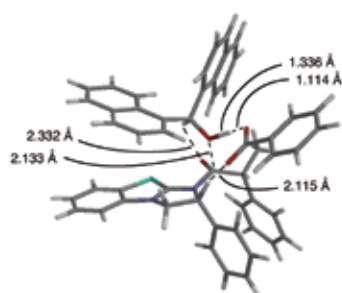
Scheme 26



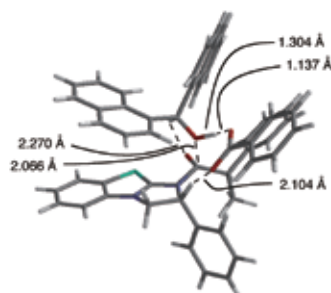
Transition State (*R*)-ts Forming (*R*)-Ester
Determined by DFT Calculation at
B3LYP/6-31G**/B3LYP/6-31G* Level



Transition State (*S*)-ts Forming (*S*)-Ester
Determined by DFT Calculation at
B3LYP/6-31G**/B3LYP/6-31G* Level



Preferred Structure (*R*)-ts
 $E_{rel} = 0$ kcal/mol



Unsuitable Structure (*S*)-ts
 $E_{rel} = +3.94$ kcal/mol

Scheme 27

11. Acknowledgements

The author is grateful to all his students in the graduate course at Tokyo University of Science for their valuable efforts. The author also expresses sincere thanks to Kenya Nakata, Assistant Professor for his great contribution to development of our asymmetric esterification, the latest result. Finally, the author would like to express his gratitude again to all involved in the research on the use of aromatic carboxylic anhydrides.

References

- 1) I. Shiina, T. Mukaiyama, *Chem. Lett.* **1992**, 2319-2320.
- 2) (a) T. Mukaiyama, I. Shiina, M. Miyashita, *Chem. Lett.* **1992**, 625-628. (b) M. Miyashita, I. Shiina, S. Miyoshi, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1516-1527.
- 3) T. Mukaiyama, M. Miyashita, I. Shiina, *Chem. Lett.* **1992**, 1747-1750.
- 4) (a) M. Miyashita, I. Shiina, T. Mukaiyama, *Chem. Lett.* **1993**, 1053-1054. (b) M. Miyashita, I. Shiina, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 210-215.
- 5) (a) T. Mukaiyama, K. Suzuki, *Chem. Lett.* **1992**, 1751-1754. (b) K. Suzuki, H. Kitagawa, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3729-3734.
- 6) I. Shiina, M. Miyashita, M. Nagai, T. Mukaiyama, *Heterocycles* **1995**, *40*, 141-148.
- 7) T. Mukaiyama, J. Izumi, M. Miyashita, I. Shiina, *Chem. Lett.* **1993**, 907-910.
- 8) (a) I. Shiina, S. Miyoshi, M. Miyashita, T. Mukaiyama, *Chem. Lett.* **1994**, 515-518. (b) I. Shiina, *Tetrahedron* **2004**, *59*, 1587-1599.
- 9) I. Shiina, T. Mukaiyama, *Chem. Lett.* **1994**, 677-680.
- 10) (a) I. Shiina, Y. Fukuda, T. Ishii, H. Fujisawa, T. Mukaiyama, *Chem. Lett.* **1998**, 831-832. (b) I. Shiina, H. Fujisawa, T. Ishii, Y. Fukuda, *Heterocycles* **2000**, *52*, 1105-1123.
- 11) (a) I. Shiina, R. Ibuka, M. Kubota, *Chem. Lett.* **2002**, 286-287. (b) I. Shiina, M. Kubota, H. Oshiumi, M. Hashizume, *J. Org. Chem.* **2004**, *69*, 1822-1830. See also, (c) I. Shiina, *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.)*, **2005**, *63*, 2-17.
- 12) (a) H. Fukui, S. Hitomi, R. Suzuki, T. Ikeda, Y. Umezaki, K. Tsuji, I. Shiina, *Tetrahedron Lett.* **2008**, *49*, 6514-6517. [Cover Feature Article] See also, (b) H. Fukui, I. Shiina, *Org. Lett.* **2008**, *10*, 3153-3156. (c) H. Fukui, I. Shiina, *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.)*, **2009**, *67*, 628-642.
- 13) (a) I. Shiina, M. Kubota, R. Ibuka, *Tetrahedron Lett.* **2002**, *43*, 7535-7539. See also, (b) I. Shiina, H. Fukui, A. Sasaki, *Nat. Protoc.* **2007**, *2*, 2312-2317. (c) I. Shiina, *Chem. Rev.* **2007**, *107*, 239-273.
- 14) (a) I. Shiina, Y. Takasuna, R. Suzuki, H. Oshiumi, Y. Komiyama, S. Hitomi, H. Fukui, *Org. Lett.* **2006**, *8*, 5279-5282. (b) I. Shiina, H. Fukui, *Chem. Commun.* **2009**, 385-400. [Feature Article]
- 15) I. Shiina, T. Katoh, S. Nagai, M. Hashizume, *Chem. Rec.* **2009**, *9*, 305-320.
- 16) I. Shiina, A. Sasaki, T. Kikuchi, H. Fukui, *Chem. Asian J.* **2008**, *3*, 462-472.
- 17) (a) I. Shiina, R. Miyao, *Heterocycles* **2008**, *76*, 1313-1328. See also, (b) I. Shiina, M. Hashizume, *Tetrahedron* **2006**, *62*, 7934-7939.
- 18) (a) I. Shiina, H. Ushiyama, Y. Yamada, Y. Kawakita, K. Nakata, *Chem. Asian J.* **2008**, *3*, 454-461. See also, (b) I. Shiina, Y. Kawakita, *Tetrahedron* **2004**, *60*, 4729-4733.
- 19) (a) I. Shiina, H. Oshiumi, M. Hashizume, Y. Yamai, R. Ibuka, *Tetrahedron Lett.* **2004**, *45*, 543-547. (b) I. Shiina, M. Hashizume, Y. Yamai, H. Oshiumi, T. Shimazaki, Y. Takasuna, R. Ibuka, *Chem. Eur. J.* **2005**, *11*, 6601-6608.
- 20) I. Shiina, T. Kikuchi, A. Sasaki, *Org. Lett.* **2006**, *8*, 4955-4958.
- 21) I. Shiina, K. Nakata, *Tetrahedron Lett.* **2007**, *48*, 8314-8317. [Cover Feature Article]
- 22) (a) I. Shiina, K. Nakata, Y. Onda, *Eur. J. Org. Chem.* **2008**, 5887-5890. (b) I. Shiina, K. Nakata, K. Ono, Y. Onda, M. Itagaki, *J. Am. Chem. Soc.* **2010**, *132*, 11629-11641.
- 23) For the asymmetric esterification, bulky fatty-chain carboxylic anhydrides, such as pivalic anhydride, are also effective as dehydrating reagents. See: (a) I. Shiina, K. Nakata, M. Sugimoto, Y. Onda, T. Iizumi, K. Ono, *Heterocycles* **2009**, *77*, 801-810. (b) I. Shiina, K. Nakata, K. Ono, M. Sugimoto, A. Sekiguchi, *Chem. Eur. J.* **2010**, *16*, 167-172.
- 24) (a) V. B. Birman, X. Li, *Org. Lett.* **2006**, *8*, 1351. (b) V. B. Birman, L. Guo, *Org. Lett.* **2006**, *8*, 4859.

(Received July 2009)

Introduction of the author :

Isamu Shiina Professor, Department of Applied Chemistry, Faculty of Science, Tokyo University of Science

[Brief career history] 1990, Graduated from Department of Applied Chemistry, Faculty of Science, Tokyo University of Science (TUS); 1992, Completed Master's Course supervised by Professor Teruaki Mukaiyama, Graduate School of Chemical Science and Technology, TUS; 1992, Assistant Professor, Research Institute for Science and Technology, TUS; 1997, Lecturer, Research Institute for Science and Technology, TUS; 1999, Lecturer, Department of Applied Chemistry, Faculty of Science, TUS; 2003, Associate Professor, Department of Applied Chemistry, Faculty of Science, TUS; Since 2008, Present post.

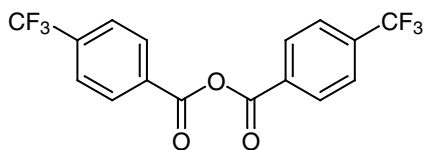
1997, Ph.D. from the University of Tokyo (UT).

1997, The Chemical Society of Japan Award for Young Chemists.

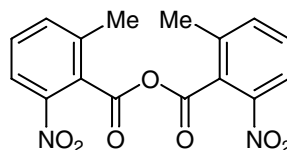
2006, Banyu Young Chemist Award.

[Specialty] Synthetic organic chemistry, Natural products synthesis

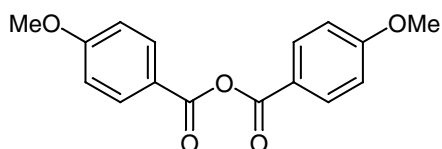
Contribution Related Compounds



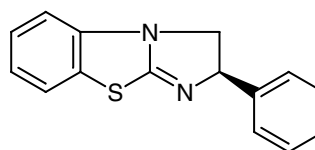
TFBA
4-Trifluoromethylbenzoic Anhydride
10g [T1593]



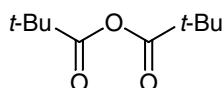
MNBA
2-Methyl-6-nitrobenzoic Anhydride
1g, 5g, 25g [M1439]



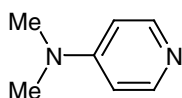
PMBA
4-Methoxybenzoic Anhydride
5g [M1973]



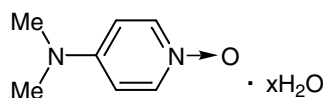
(+)-BTM
(+)-Benzotetramisole
200mg, 1g [B3296]



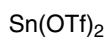
Pivalic Anhydride
25ml, 250ml [P1414]



DMAP
4-Dimethylaminopyridine
25g, 500g [D1450]



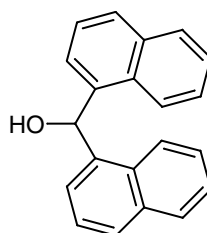
DMAPO
4-(Dimethylamino)pyridine N-Oxide Hydrate
1g, 5g [D3220]



Tin(II) Trifluoromethanesulfonate
1g, 5g, 25g [T1194]



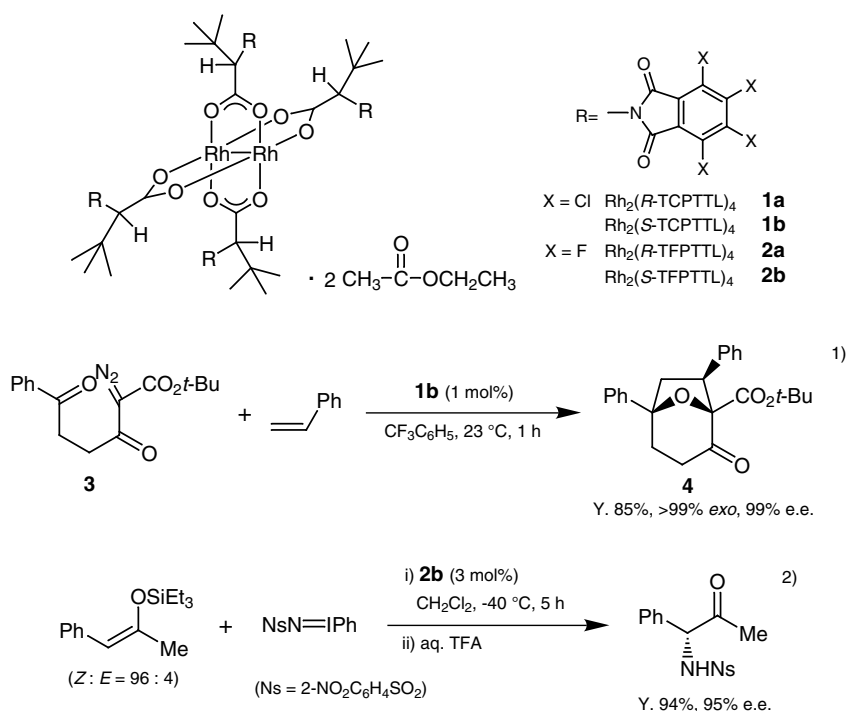
Hafnium(IV) Trifluoromethanesulfonate
1g, 5g [T1708]



Bis(α -naphthyl)methanol
5g [D3750]

Useful Chiral Dirhodium(II) Complex Catalyst

- T2658 Tetrakis[*N*-tetrachlorophthaloyl-(*R*)-*tert*-leucinato]dirhodium Bis(ethyl Acetate) Adduct (**1a**)
50 mg
- T2659 Tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinato]dirhodium Bis(ethyl Acetate) Adduct (**1b**)
100 mg
- T2660 Tetrakis[*N*-tetrafluorophthaloyl-(*R*)-*tert*-leucinato]dirhodium Bis(ethyl Acetate) Adduct (**2a**)
50 mg
- T2661 Tetrakis[*N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinato]dirhodium Bis(ethyl Acetate) Adduct (**2b**)
100 mg



Hashimoto *et al.* have developed chiral dirhodium(II) complexes, $\text{Rh}_2(\textit{R}\text{-PTTL})_4$, $\text{Rh}_2(\textit{S}\text{-PTTL})_4$, $\text{Rh}_2(\textit{R}\text{-TCPTTL})_4$, $\text{Rh}_2(\textit{S}\text{-TCPTTL})_4$, $\text{Rh}_2(\textit{R}\text{-TFPTTL})_4$ and $\text{Rh}_2(\textit{S}\text{-TFPTTL})_4$, and reported their usefulness. According to their results, intramolecular C-H insertion reactions, 1,3-dipolar cycloaddition of carbonyl ylides and amination of silyl enol ethers are catalyzed by these dirhodium(II) complexes to proceed highly enantioselectively and give corresponding products in high yields.

Typical Procedure¹⁾:

A solution of diazo compound **3** (60.5 mg, 0.20 mmol) and styrene (62.5 mg, 0.60 mmol) in $\text{CF}_3\text{C}_6\text{H}_5$ (1.0 mL) is added via syringe pump over 1 h to a stirred solution of **1b** (3.95 mg, 0.002 mmol, 1 mol%) in $\text{CF}_3\text{C}_6\text{H}_5$ (1.0 mL). After complete addition, the reaction mixture is concentrated *in vacuo*, and the residue is purified by column chromatography (silica gel, hexane:EtOAc = 6:1) to provide **4** (64.5 mg, Y. 85%) as a white solid.

References

- Enantioselective 1,3-dipolar cycloaddition of carbonyl ylide
N. Shimada, M. Anada, S. Nakamura, H. Nambu, H. Tsutsui, S. Hashimoto, *Org. Lett.* **2008**, *10*, 3603.
- Enantioselective amination of silyl enol ether
M. Anada, M. Tanaka, T. Washio, M. Yamawaki, T. Abe, S. Hashimoto, *Org. Lett.* **2007**, *9*, 4559.

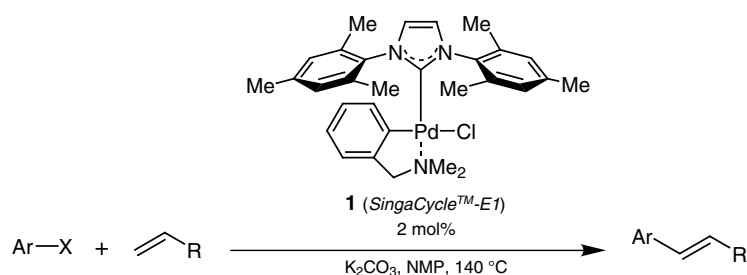
Related Compounds

- T2054 Tetrakis[*N*-phthaloyl-(*R*)-*tert*-leucinato]dirhodium Bis(ethyl Acetate) Adduct 100mg
- T2055 Tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinato]dirhodium Bis(ethyl Acetate) Adduct 100mg

SingaCycle™-E1 –Catalyst for the Heck-Mizoroki Reaction

C2347 Chloro[(1,3-dimesitylimidazol-2-ylidene)(*N,N*-dimethylbenzylamine)palladium(II)]
(SingaCycle™-E1) (1) 200mg 1g 5g

*This product is not available in Canada and Americas.



Ar—X	Olefin	Product	Yield (%)
			92
			72
			93
			84

A highly active, versatile and practical catalyst **1** for the Heck-Mizoroki Reaction has been developed by Ying *et al.* The palladium complex **1** consists of a sterically demanding *N*-heterocyclic carbene spectator ligand and a palladacycle as disposable part, releasing *in situ* the catalytically highly active mono-ligated Pd(0) species. Compound **1** is a robust and stable, ready to use catalyst which can be conveniently handled under air. **1** is available from discovery- to production scale amounts.

Typical procedure: ^{1a)}

Aryl Bromide (1 mmol), olefin (1.2 mmol), K₂CO₃ (2.0 mmol) and 2 mol% NMP solution of SingaCycle™-E1 (400 μL) are added to a vial with a magnetic stir bar. The atmosphere above the reaction mixture is purged with Ar over 30 sec. The vial is closed with a screw cap, and heated at 140 °C with vigorous stirring over 18 h. After cooling, the reaction mixtures are filtered under dilution with CH₂Cl₂ (total: 20 mL). The crude product is loaded directly over a short pad of silica gel and purified by flash chromatography.

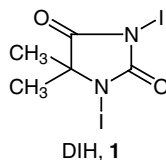
References

- 1) An NHC-ligated palladacycle as an active catalyst for the Heck-Mizoroki reaction
a) E. A. B. Kantchev, G.-R. Peh, C. Zhang, J. Y. Ying, *Org. Lett.* **2008**, *10*, 3949. b) G.-R. Peh, E. A. B. Kantchev, C. Zhang, J. Y. Ying, *Org. Biomol. Chem.* **2009**, *7*, 2110. c) J. Y. Ying, E. A. B. Kantchev, PCT Int. Appl. WO 08 156451, **2008**. d) E. A. B. Kantchev, J. Y. Ying, *Organometallics* **2009**, *28*, 289.

Highly Effective Iodinating Reagent

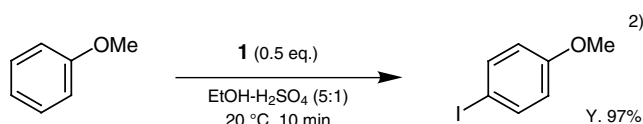
D3657 1,3-Diiodo-5,5-dimethylhydantoin (= DIH) (1)

5g 25g

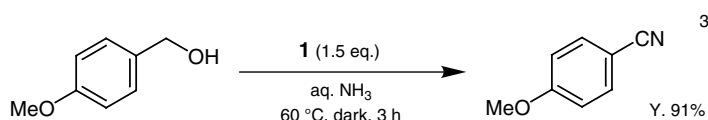


1,3-Diiodo-5,5'-dimethylhydantoin (DIH, **1**), which was first reported by Orazi, is an useful iodinating reagent.¹⁾ **1** has higher reactivity and selectivity than molecular iodine or *N*-iodosuccinimide (NIS), which are frequently used for iodination reactions. **1** is a pale yellow solid that does not sublime like molecular iodine, and has low toxicity, which makes it easier to handle. In addition, dimethylhydantoin, which is formed after the reaction, can easily be removed by aqueous extraction.

1 reacts smoothly at room temperature with aromatic compounds in the presence of sulfuric acid to give the corresponding iodinate in a high regioselectivity and a high yield. Moreover, even low-activated substances such as nitrobenzene can easily be iodinated by using sulfuric acid as solvent.²⁾



Togo *et al.* have reported an efficient method for preparing nitriles.³⁾ According to their results, primary alcohols, and primary, secondary, and tertiary amines can be easily and efficiently converted into the corresponding nitriles in aqueous ammonia using **1**.



Moreover, Togo *et al.* have also reported the efficient synthesis of 2-substituted-2-oxazolines by the reaction of 2-aminoethanol and aldehydes using **1**.⁴⁾ Moreover, it is notable that chiral bis-2-oxazolines, which are quite useful as chiral ligands in asymmetric synthesis, can also be prepared in moderate yields with chiral 2-phenylglycinol under the same conditions.

Typical Procedure²⁾:

Sulfuric acid (2 mL) is added under stirring and cooling to a solution of anisole (1.1g, 10 mmol) in ethanol (15 mL), and DIH (**1**; 1.9 g, 5 mmol) is then added in 3 portions over a period of 2-3 min. When the reaction is complete, the mixture is diluted with 3% solution of Na₂SO₃ (50 mL), and the precipitate is filtered off, washed with water, dried, and recrystallized from appropriate solvent. Yield of 4-iodoanisole 97%.

References

- 1) O. O. Orazi, R. A. Corral, H. E. Bertorello, *J. Org. Chem.* **1965**, *30*, 1101.
- 2) V. K. Chaikovskii, V. D. Filimonov, A. A. Funk, V. I. Skorokhodov, V. D. Ogorodnikov, *Russ. J. Org. Chem.* **2007**, *43*, 1291.
- 3) M. Ishihara, H. Togo, *Tetrahedron* **2007**, *63*, 1474; S. Iida, H. Togo, *Tetrahedron* **2007**, *63*, 8274.
- 4) S. Takahashi, H. Togo, *Synthesis* **2009**, 2329.

Related Compounds

B1604	Benzyltrimethylammonium Dichloroiodate	5g	25g
I0074	<i>N</i> -Iodosuccinimide (= NIS)	5g	25g 100g
I0604	Iodine		25g 500g

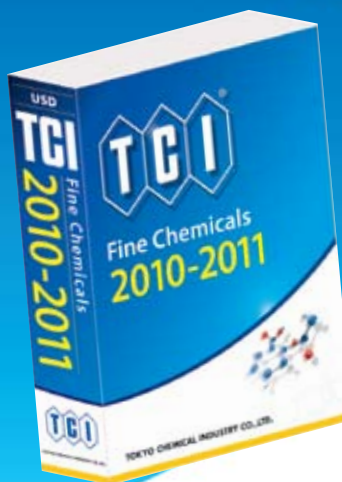
New TCI Catalog 2010-2011

Available Now. Request Your Free Copy!

21,000 Fine Chemicals
1,300 New Products

- Synthetic Organic Chemicals
- Functional Materials
- Biochemicals
- Analytical Reagents
- Standard Materials

▶▶ Contact our local offices listed below.



**Ordering and
Customer Service**

TCI EUROPE N.V.

Tel : +32 (0)3 735 07 00
Fax : +32 (0)3 735 07 01
E-mail : sales@tcieurope.eu
Website: www.tcieurope.eu
Address: Boerenveldseweg 6 - Haven 1063, 2070 Zwijndrecht
Belgium

TCI Deutschland GmbH

Tel : +49 (0)6196 998678-0
Fax : +49 (0)6196 998678-1
E-mail : sales@tcideutschland.de
Website: www.tcieurope.eu/de/
Address: Mergenthalerallee 79-81, 65760 Eschborn, Germany

Tokyo Chemical Industry UK Ltd.

Tel : +44 (0)1865 784560
Fax : +44 (0)1865 784561
E-mail : sales@tci-uk.co.uk
Website: www.tci-uk.co.uk
Address: The Magdalen Centre, Robert Robinson Avenue
The Oxford Science Park, Oxford OX4 4GA
United Kingdom

TCI AMERICA

Tel : 800-423-8616 • 503-283-1681
Fax : 888-520-1075 • 503-283-1987
E-mail : sales@tciamerica.com
Website: www.tciamerica.com
Address: 9211 N. Harborside Street, Portland, OR 97203, U.S.A.

TOKYO CHEMICAL INDUSTRY CO., LTD.

Tel : +81-3-5640-8878
Fax : +81-3-5640-8902
E-mail : globalbusiness@tokyokasei.co.jp
Website: www.tci-asiapacific.com
Address: 4-10-2 Nihonbashi-honcho, Chuo-ku, Tokyo 103-0023
Japan

梯希爱(上海)化成工业发展有限公司

Tel : 800-988-0390 • 021-6712-1386
Fax : 021-6712-1385
E-mail : sales@tcishanghai.com.cn
Website: www.tcishanghai.com.cn
Address: 上海市化学工业区普工路96号, 邮编201507

TCI Chemicals (India) Pvt. Ltd.

Tel : 044-4261 2444
Fax : 044-4261 1065
E-mail : sales@tci-india.com
Website: www.tci-india.com
Address: Bharanee Subalesh building, B1, H-71, 5th Main Road
Annanagar(East), Chennai-600102, Tamilnadu, India

• The chemical, physical and toxicological properties of some chemicals have not been thoroughly investigated. Please handle with care.

• Chemicals itemized in this catalog are for testing or research purpose only. Therefore, please note those chemicals are not guaranteed in the user's favor relating to various problems under the Patent Law that might occur through their use.

• Availability or specification of the listed products are subject to change without prior notice.

• Reproduction forbidden without the prior written consent of Tokyo Chemical Industry Co., Ltd.

Printed in Japan