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Catalytic Enantioselective Amination of Silyl Enol Ethers Using Chiral Dirhodium(II) Carboxylates: Asymmetric Formal Synthesis of (−)-Metazocine†

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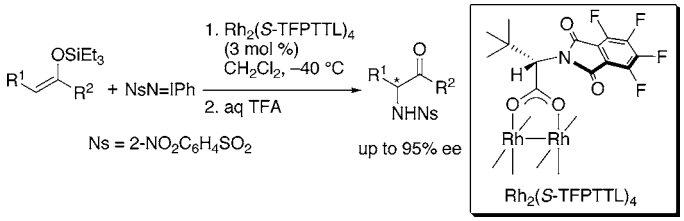
ABSTRACT



Dirhodium(II) tetrakis[*N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-TFPTTL)$_4$, is an exceptionally efficient catalyst for enantioselective aminations of silyl enol ethers derived from acyclic ketones or α,β-enones with [*N*-(2-nitrophenylsulfonyl)imino]phenyliodinane (NsN═IPh), providing *N*-(2-nitrophenylsulfonyl)-α-amino ketones in high yields and with enantioselectivities of up to 95% ee. The effectiveness of the present catalytic protocol has been demonstrated by an asymmetric formal synthesis of (−)-metazocine.

The catalytic asymmetric amination of ketone-derived enol ethers is one of the most powerful methods for the preparation of enantioenriched α-amino ketones, which are versatile building blocks for the synthesis of biologically active compounds such as *syn*- and *anti*-α-amino alcohols.[1] Recent advances[2−6] in this field include Sharpless asymmetric aminohydroxylation of silyl enol ethers,[2] Cu(II)- and Ag(I)-catalyzed electrophilic amination of silyl enol ethers with azodicarboxylate derivatives,[3,4] and Ag(I)-catalyzed regio- and enantioselective *N*-nitroso aldol reaction of tin(IV) enolates.[5] In this context, the aziridination of silyl enol ethers followed by ring opening of aziridine intermediates provides an attractive and practical entry to α-amino ketone derivatives.[7] While high levels of enantiocontrol in aziridinations of alkenes have already been achieved using a variety of different chiral transition-metal catalysts,[8] the goal for those of enol derivatives remains elusive.[9] To our knowledge,

† This paper is dedicated to the the memory of the late Dr. Yoshihiko Ito, Professor Emeritus of Kyoto University.

(1) For recent reviews on enantioselective amination of carbonyl compounds, see: (a) Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975−978. (b) Greck, C.; Drouillat, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, 1377−1385. (c) Erdik, E. *Tetrahedron* **2004**, *60*, 8747−8782. (d) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292−4300. (e) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465−1492.

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(4) Yamashita, Y.; Ishitani, H.; Kobayashi, S. *Can. J. Chem.* **2000**, *78*, 666−672.

(5) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360−5361.

(6) (a) Recently, Jørgensen and co-workers reported L-proline-catalyzed direct asymmetric α-aminations of alkyl methyl ketones with azodicarboxylates, which led to a mixture of the expected 3-hydrazino ketones (up to 99% ee) and 1-hydrazino regioisomers (76:24∼91:9 regioselectivity): Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254−6255. See also: (b) Thomassigny, C.; Prim, D.; Greck, C. *Tetrahedron Lett.* **2006**, *47*, 1117−1119.

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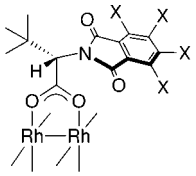
only two examples have been reported. Adam and co-workers were the first to demonstrate asymmetric induction (up to 52% ee) in the reaction of enol acetates or silyl enol ethers and [(*p*-tolylsulfonyl)imino]phenyliodinane (TsN═IPh, **2a**) using 5.5−6 mol % of copper(I)−bis(oxazoline) or copper(I)−diimine complexes as chiral catalysts.[10] Thereafter, Che and co-workers explored the amination of silyl enol ethers with TsN═IPh in the presence of 12.5 mol % of chiral ruthenium(II)−salen catalyst, in which high enantioselectivity (97% ee) was achieved only with 1-trimethylsiloxy-1-cyclohexene, albeit in poor substrate conversion (23%).[11]

We recently reported that the enantioselective benzylic C−H amination of aromatic hydrocarbons with [*N*-(4-nitrophenylsulfonyl)imino]phenyliodinan (*p*NsN═IPh, **2b**) catalyzed by chiral dirhodium(II) carboxylates provides sulfonamides in up to 84% ee.[12] In this process,

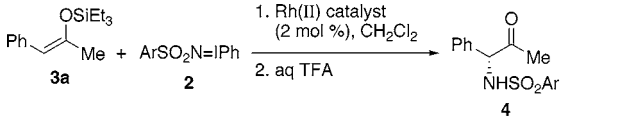


X = Cl: Rh_2(*S*-TCPTTL)$_4$ (**1a**)
X = F: Rh_2(*S*-TFPTTL)$_4$ (**1b**)
X = H: Rh_2(*S*-PTTL)$_4$ (**1c**)

Rh_2(*S*-TCPTTL)$_4$ (**1a**), characterized by the substitution of chlorine atoms for four hydrogen atoms on the phthalimido group in the parent dirhodium(II) complex, Rh_2(*S*-PTTL)$_4$ (**1c**), proved to be the catalyst of choice in terms of product yield and enantioselectivity as well as catalytic activity.[13] Herein, we report the first successful example of catalytic enantioselective amination of silyl enol ethers derived from acyclic ketones or enones with sulfonyliminoiodinanes, in which the fluorinated complex Rh_2(*S*-TFPTTL)$_4$ (**1b**) has emerged as the catalyst of choice for achieving enantioselectivities as high as 95% ee.

At the outset, we explored the amination of silyl enol ether **3a** (*Z*/*E* = 96:4) derived from phenylacetone with 1.05 equiv of *p*NsN═IPh (**2b**) in the presence of 2 mol % of Rh_2(*S*-TCPTTL)$_4$ (**1a**). The reaction proceeded smoothly in CH_2Cl_2 at 0 °C and, after treatment with 90% aqueous trifluoroacetic acid (TFA), gave α-amino ketone **4b** in 94% yield (Table 1, entry 1). The enantioselectivity of this reaction

Table 1. Rh(II)-Catalyzed Enantioselective Amination of Silyl Enol Ether **3a** with **2**[a]



3a + **2** → (1. Rh(II) catalyst (2 mol %), CH_2Cl_2; 2. aq TFA) → **4**

2a: Ar = 4-MeC_6H_4
2b: Ar = 4-$NO_2C_6H_4$
2c: Ar = 2-$NO_2C_6H_4$
2d: Ar = 2,4-$(NO_2)_2C_6H_3$

4a: Ar = 4-MeC_6H_4
4b: Ar = 4-$NO_2C_6H_4$
4c: Ar = 2-$NO_2C_6H_4$
4d: Ar = 2,4-$(NO_2)_2C_6H_3$

entry	2	Rh(II)	temp (°C)	time (h)	product	yield[b] (%)	ee[c] (%)
1	**2b**	**1a**	0	1	**4b**	94	57
2	**2c**	**1a**	0	0.5	**4c**	94	86
3	**2d**	**1a**	0	2	**4d**	95	60[d]
4	**2a**	**1a**	0	6	**4a**	55	77
5[e]	**2c**	**1a**	0	24	**4c**	NR[f]	
6	**2c**	**1b**	0	0.5	**4c**	93	86
7	**2c**	**1c**	0	6	**4c**	82	67
8[g]	**2c**	**1b**	−40	5	**4c**	94	95
9[g]	**2c**	**1a**	−40	18	**4c**	93	88

[a] All reactions were performed on a 0.2 mmol scale (0.1 M) with 1.05 equiv of **2**. [b] Yield of isolated products. [c] Determined by HPLC. [d] The preferred absolute stereochemistry was not determined. [e] *Z*/*E* = 1:>99 of **3a** was used. [f] No reaction. [g] 3 mol % of the catalyst was used.

was determined to be 57% ee by HPLC analysis (Daicel Chiralpak AD-H). The preferred absolute stereochemistry of **4b** [$[\alpha]^{24}_D$ −103.1 (*c* 0.89, $CHCl_3$) for 57% ee] was established as *R* by chemical correlation.[14] A survey of nitrene precursors revealed that [(2-nitrophenylsulfonyl)imino]-phenyliodinane (NsN═IPh, **2c**) was greatly superior in terms of reaction rate and enantioselectivity (86% ee, entry 2).[15] Although the use of [(2,4-dinitrophenylsulfonyl)imino]-phenyliodinane (DNsN═IPh, **2d**) resulted in levels of product yield and asymmetric induction similar to those found with **2b** (entry 3), the use of TsN═IPh (**2a**), the most commonly used nitrene precursor in this field, markedly diminished the product yield (entry 4).[16] Interestingly, the amination of (*E*)-isomer of **3a** (*Z*/*E* = 1:>99) with **2c** did not work even after 24 h (entry 5). We then evaluated the performance of [Rh_2(*S*-TFPTTL)$_4$] (**1b**)[17] and [Rh_2(*S*-PTTL)$_4$] (**1c**).[18,19] While [Rh_2(*S*-TFPTTL)$_4$] exhibited essentially the same rate and

(8) For reviews on transition-metal-catalyzed enantioselective aziridination of alkenes with (arylsulfonylimino)phenyliodinanes and arylsulfonyl azides, see: (a) Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, Chapter 17, pp 607−618. (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2919. (c) Katsuki, T. *Chem. Lett.* **2005**, *34*, 1304−1309.

(9) For enantioselective amination of silyl enol ethers using stoichiometric amounts of chiral nitridomanganese complexes, see: (a) Minakata, S.; Ando, T.; Nishimura, M.; Ryu, I.; Komatsu, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3392−3394. (b) Svenstrup, N.; Bøgevig, A.; Hazell, R. G.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans 1* **1999**, 1559−1565.

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(11) Liang, J.-L.; Yu, X.-Q.; Che, C.-M. *Chem. Commun.* **2002**, 124−125.

(12) Yamawaki, M.; Tsutsui, H.; Kitagaki, S.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 9561−9564.

(13) Recently, Reddy and Davies reported enantioselective benzylic C−H amination using dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-(1-adamantyl)glycinate], Rh_2(*S*-TCPTAD)$_4$, as a catalyst; see: Reddy, R. P.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 5013−5016.

(14) For the determination of absolute stereochemistry, see the Supporting Information.

(15) A survey of solvents revealed that CH_2Cl_2 was the optimal solvent for this transformation. While toluene and benzotrifluoride exhibited nearly the same yields and enantioselectivities as CH_2Cl_2, reaction times to complete the reaction in these solvents were extended (toluene, 9 h, 92% yield, 86% ee; $PhCF_3$, 6 h, 95% yield, 85% ee).

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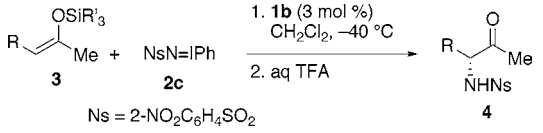
(17) Tsutsui, H.; Yamaguchi, Y.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2003**, *14*, 817−821.

(18) Minami, K.; Saito, H.; Tsutsui, H.; Nambu, H.; Anada, M.; Hashimoto, S. *Adv. Synth. Catal.* **2005**, *347*, 1483−1487 and references cited therein.

enantioselectivity as those found with Rh_2(*S*-TCPTTL)$_4$ (entry 6), Rh_2(*S*-PTTL)$_4$ was less effective in terms of both reactivity and enantioselectivity (entry 7). An examination of the temperature profile demonstrated that optimal enantiocontrol was achieved with Rh_2(*S*-TFPTTL)$_4$ at −40 °C, affording α-amino ketone **4c** in 94% yield with 95% ee, although 3 mol % of the catalyst was necessary to achieve full conversion within reasonable reaction times (entry 8). In contrast, catalysis with Rh_2(*S*-TCPTTL)$_4$ under the same conditions required significantly longer reaction times to reach completion and resulted in 88% ee (entry 9).

Having identified the effectiveness of the combination of Rh_2(*S*-TFPTTL)$_4$ as the catalyst and **2c** as the nitrene precursor, the applicability of this catalytic system to a range of silyl enol ethers was then investigated (Table 2). The size

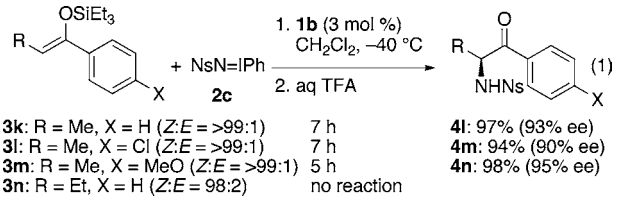
Table 2. Enantioselective Amination Reaction of Silyl Enol Ethers Catalyzed by **1b**



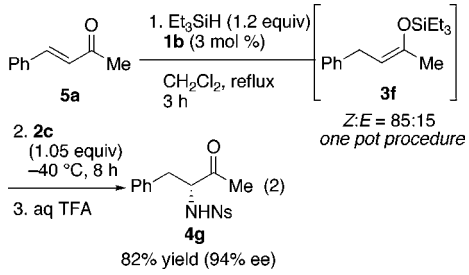
	silyl enol ether					product		
entry		R	SiR'_3	*Z*/*E* ratio	time (h)		yield[a] (%)	ee[b] (%)
1	**3a**	Ph	Et_3Si	96:4	5	**4c**	94	95
2	**3b**	Ph	Me_3Si	96:4	4	**4c**	94	93
3	**3c**	Ph	*t*-$BuMe_2Si$	96:4	6	**4c**	94	95
4	**3d**	4-ClC_6H_4	Et_3Si	96:4	6	**4e**	95	84[c]
5	**3e**	4-$MeOC_6H_4$	Et_3Si	96:4	4	**4f**	91	78[c]
6	**3f**	$PhCH_2$	Et_3Si	>99:1	8	**4g**	94	95
7	**3g**	4-$ClC_6H_4CH_2$	Et_3Si	86:14	9	**4h**	80	90[c]
8	**3h**	4-$MeOC_6H_4CH_2$	Et_3Si	87:13	8	**4i**	82	90
9	**3i**	$CH_3(CH_2)_3$	Et_3Si	88:12	3	**4j**	81	47[c]
10	**3j**	*c*-$C_6H_{11}CH_2$	Et_3Si	95:5	24	**4k**	89	56[c]

[a] Yield of isolated products. [b] Determined by HPLC. [c] The preferred absolute stereochemistry was not determined.

of the trialkylsilyl group had little impact on product yield and enantioselectivity (entries 1−3). However, switching the R substituent from a phenyl group to *p*-chloro- or *p*-methoxyphenyl groups diminished enantioselectivity (84% and 78% ee, entries 4 and 5). While the amination of benzyl-substituted silyl enol ethers **3f**−**h** gave the respective α-amino ketones **4g**−**i** in high yield with high levels of enantioselectivity (90−95% ee, entries 6−8),[20] use of silyl enol ethers **3i**,**j** derived from 2-heptanone and 4-cyclohexyl-2-butanone resulted in only modest enantioselection (47% and 56% ee, entries 9 and 10). The amination of silyl enol ether **3k** derived from propiophenone provided α-amino ketone **4l** in 97% yield with 93% ee, in which the preferred absolute stereochemistry of **4l** was opposite to that of **4c** (eq 1).[14] In this system (R = Me), high enantioselectivity was consistently observed with either electron-withdrawing or electron-donating groups present at the para position on the benzene ring (90% and 95% ee, respectively), whereas no reaction proceeded with **3n** bearing a more sterically demanding ethyl group.



During the course of the above studies, we found that dirhodium(II) carboxylates are effective catalysts for 1,4-hydrosilylation of α,β-enones.[21,22] This observation led us to explore the feasibility of using Rh_2(*S*-TFPTTL)$_4$ to mediate one-pot sequential 1,4-hydrosilylation/enantioselective amination of α,β-enones.[23] Upon completion of the 1,4-hydrosilylation reaction of benzalacetone (**5a**) with triethylsilane in the presence of 3 mol % of Rh_2(*S*-TFPTTL)$_4$ (performed in CH_2Cl_2 under reflux for 3 h), the reaction mixture (*Z*/*E* ratio of **3f** = 85:15) was treated with **2c** (1.05 equiv) at −40 °C for 8 h in the same reaction vessel. After the usual workup, the desired α-amino ketone **4g** was obtained in 82% overall yield with 94% ee, very comparable to that obtained in the amination of **3f** (eq 2 vs Table 2, entry 6). While the mechanistic profile of the dirhodium(II) carboxylate-catalyzed 1,4-hydrosilylation is not clear at present,[22] this result strongly suggested that the integrity of the ligands on the dirhodium framework was not compromised during the 1,4-hydrosilylation process.



The *N*-2-nitrophenylsulfonyl group is synthetically advantageous since the alkylation of *N*-monosubstituted Ns-amides and deprotection proceed under mild conditions.[24] To demonstrate the utility of the present catalytic protocol, we thus explored a novel, catalytic approach to (−)-metazocine

(19) For a practical synthesis of Rh_2(*S*-PTTL)$_4$, see: Tsutsui, H.; Abe, T.; Nakamura, S.; Anada, M.; Hashimoto, S. *Chem. Pharm. Bull.* **2005**, *53*, 1366−1368.

(20) No reaction was observed when the (*E*)-isomer of **3f** (*Z*/*E* = 1:>99) was used.

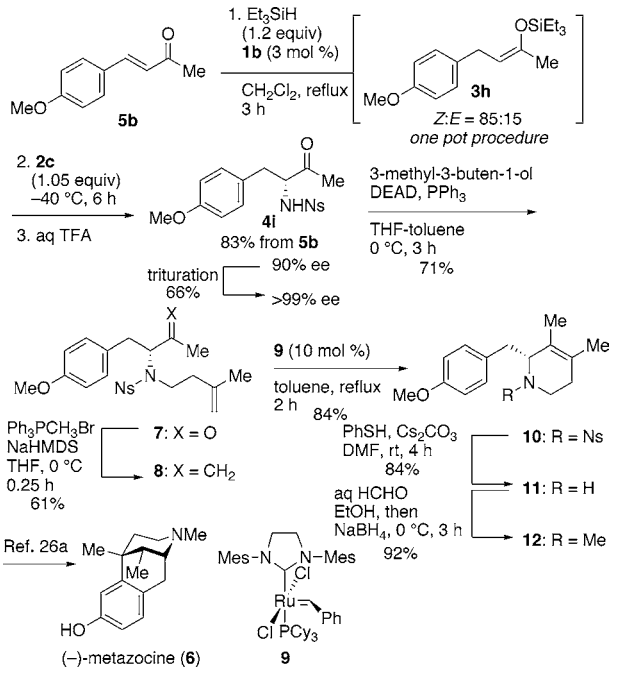
(21) Anada, M.; Tanaka, M.; Suzuki, K.; Nambu, H.; Hashimoto, S. *Chem. Pharm. Bull.* **2006**, *54*, 1622−1623.

(22) For a seminal work on Rh(II)-catalyzed hydrosilylation reactions of 1-alkynes and 1-alkenes, see: (a) Doyle, M. P.; High, K. G.; Nesloney, C. L.; Clayton, T. W., Jr.; Lin, J. *Organometallics* **1991**, *10*, 1225−1226. (b) Doyle, M. P.; Devora, G. A.; Nefedov, A. O.; High, K. G. *Organometallics* **1992**, *11*, 549−555.

(23) For a recent review on single-pot catalysis of fundamentally different transformations, see: Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754−3760.

(24) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373−6374. For a review on the nitrophenylsulfonamide chemistry, see: (b) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353−359.

Scheme 1. Asymmetric Formal Synthesis of (−)-Metazocine



(**6**), a benzomorphan analgesic (Scheme 1).[25−28] The one-pot 1,4-hydrosilylation/enantioselective amination of 4-methoxybenzalacetone (**5b**) led to the formation of α-amino ketone **4i** in 83% yield with 90% ee [mp 127−128 °C; $[\alpha]^{24}_D$ −72.5 (*c* 1.14, $CHCl_3$) for 90% ee]. Fortunately, we found that trituration of **4i** (90% ee) in methanol gave crystals of 75% ee (32%, mp 129−132 °C), while the mother liquor contained **4i** with >99% ee [66%, mp 125−126 °C, $[\alpha]^{24}_D$ −81.9 (*c* 0.89, $CHCl_3$)]. *N*-Alkylation of **4i** (>99% ee) with 3-methyl-3-buten-1-ol under Mitsunobu conditions[24,29] gave the *N*,*N*-disubstituted α-amino ketone **7** in 71% yield, which, upon Wittig methylenation, furnished diene **8** in 61% yield without racemization. Ring-closing metathesis (RCM) of **8** in the presence of 10 mol % of the second-generation Grubbs catalyst (**9**)[30] proceeded smoothly in toluene under reflux to give the tetrasubstituted alkene **10** in 84% yield.[31] Removal of the Ns group under standard Fukuyama conditions[24] and subsequent reductive alkylation produced tetrahydropyridine **12** [$[\alpha]^{22}_D$ +6.4 (*c* 0.98, ether)] in 77% yield. This product exhibited spectroscopic data identical to the intermediate in Meyers' asymmetric synthesis of (+)-metazocine, except for the sign of optical rotation [lit.,[26a] $[\alpha]_D^{25}$ −6.8 (*c* 1.5, ether) for (*S*)-**12**]. Thus, Grewe cyclization[32] of **12** with HBr as reported by Meyers and co-workers[26a] completed the catalytic asymmetric synthesis of (−)-metazocine (**6**), which is a much more potent analgesic than the (+)-enantiomer.[33]

In summary, we have demonstrated that Rh_2(*S*-TFPTTL)$_4$ is an exceptionally effective catalyst for enantioselective aminations of silyl enol ethers derived from acyclic ketones with NsN═IPh. Furthermore, we have developed a novel, one-pot sequential 1,4-hydrosilylation/amination procedure for the enantioselective synthesis of *N*-(2-nitrophenylsulfonyl)-α-amino ketones from α,*β*-enones. The effectiveness of the present catalytic protocol has been demonstrated by an asymmetric formal synthesis of (−)-metazocine. Further studies on the scope of the reaction as well as mechanistic and stereochemical studies are currently in progress.

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

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(26) For chiral auxiliary-based asymmetric syntheses of (+)-**6**, see: (a) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974−7978. (b) Génisson, Y.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1993**, *58*, 2052−2057. (c) Comins, D. L.; Zhang, Y.; Joseph, S. P. *Org. Lett.* **1999**, *1*, 657−659.
(27) For catalytic asymmetric synthesis of an intermediate for (−)-**6**, see: (a) Kitamura, M.; Hsiao, Y.; Noyori, R. *Tetrahedron Lett.* **1987**, *28*, 4829−4832. (b) Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J. Org. Chem.* **1994**, *59*, 297−310.
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