

Variable C₂-Symmetric Analogues of *N*-Hydroxyphthalimide as Enantioselective Catalysts for Aerobic Oxidation: Kinetic Resolution of Oxazolidines**

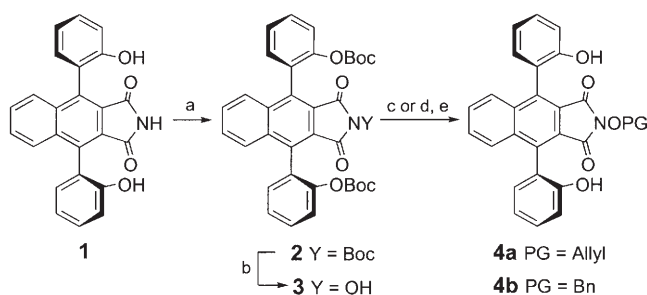
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In memory of André Rassat

During the past decade, aerobic oxidation catalyzed by *N*-hydroxyphthalimide (NHPI) or its analogues has emerged as a powerful tool in organic synthetic methodology. This technique allows the selective and mild oxidation or, more generally, the functionalization of a broad variety of organic compounds, including alkanes, benzylic hydrocarbons, alkenes, alkynes, alcohols, ethers, amides, and acetals,^[1,2] under environmentally benign conditions. Catalysis proceeds via an intermediate phthalimide *N*-oxyl radical (PINO): a reactive nitroxide-type radical able to abstract a hydrogen atom from the substrate. The resulting carbon-centered radical then combines with molecular oxygen.^[3] In this context, we reported previously the synthesis of axially chiral analogues of NHPI. These analogues exhibited modest enantioselectivities in some representative asymmetric oxidation reactions, such as the desymmetrization of 2-substituted indanes and the kinetic resolution of racemic acetals.^[4] Herein we report a straightforward approach to the synthesis of variable C₂-symmetric analogues of NHPI from diphenol **1**, which can be obtained in high diastereomeric purity by thermal isomerization in the solid state.^[5] We reported previously an efficient resolution of (±)-**1** via the corresponding *N*(α)-Boc-tryptophan diesters; each enantiomer of **1** is now readily available with > 99% *ee*. Additionally, the absolute configuration of the two enantiomers has been established.^[6]

The principle of the present approach is the selective transformation of the imide function of **1** into an *N*-hydroxyimide,^[7] and the use of the phenolic moieties as handles to introduce variable substituents. First, **1** was converted into the tris-Boc-functionalized derivative **2** with di-*tert*-butyldicarbonate (Boc₂O) in the presence of DMAP. Gratifyingly, **2** reacted with aqueous hydroxylamine (1 equiv)

to give cleanly the *N*-hydroxyimide **3** as a result of nucleophilic attack of hydroxylamine solely at the imide moiety of **2** without affecting the phenolic Boc groups. Allylic or benzylic protection of the *N*-hydroxyimide functionality was then followed by acidic removal of the phenolic Boc groups. The precatalysts **4a** and **4b** were thus obtained from **1** in 90 and 88% overall yield, respectively (Scheme 1). The whole



Scheme 1. a) Boc₂O (3 equiv), DMAP (10 mol %), CH₃CN, RT; b) aq NH₂OH (1 equiv), CH₃CN, RT; c) allyl bromide, K₂CO₃, acetone, RT; d) benzyl bromide, K₂CO₃, DMSO, RT; e) TFA/CH₂Cl₂ (1:1), RT. Bn = benzyl, Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, DMSO = dimethyl sulfoxide, TFA = trifluoroacetic acid.

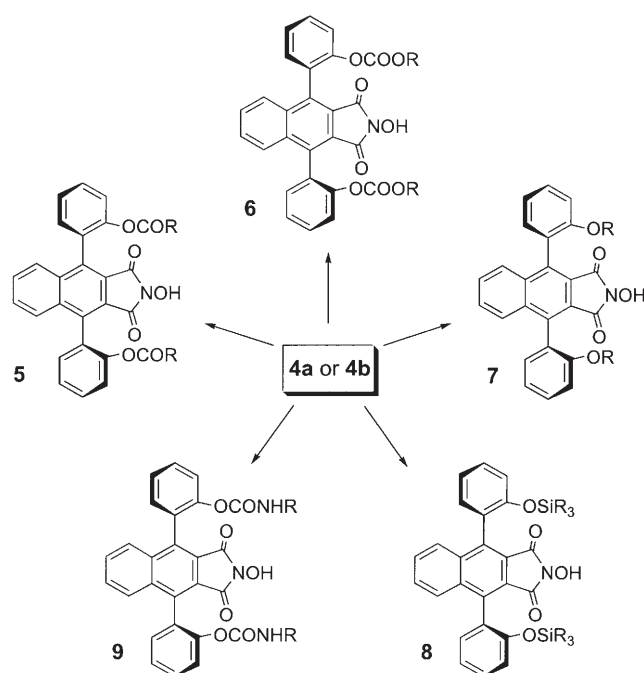
sequence was carried out at room temperature, thus avoiding thermal atropisomerization of configurationally fragile compounds.^[5,6] Compounds (*aS,aS*)-**4a** and (*aS,aS*)-**4b** were obtained from (*aS,aS*)-**1** (> 99% *ee*) with no loss of enantiomeric purity.

Some transformations of **4a** and **4b** into functionally and structurally diverse C₂-symmetric NHPI analogues are depicted in Scheme 2. Thus, **4a** and **4b** react readily with acid chlorides to give catalysts of type **5** after deprotection of the *N*-hydroxyimide. Similarly, chlorosilanes, alkyl halides, chlorosilanes, and isocyanates react as electrophiles to give catalysts of type **6**, **7**, **8**, and **9**, respectively. As mentioned previously, atropisomerization can be avoided by conducting the reactions at or below room temperature. In this way a broad variety of enantiopure catalysts are readily available from enantiopure **4a** or **4b**. Some representative examples are given in Table 1. Thus, **4b** reacted quantitatively with benzoyl chloride (2 equiv) in the presence of Et₃N. Removal of the benzyl protecting group under standard conditions then gave diester **5a** (Table 1, entry 1). Compound **4a** was treated

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Scheme 2. Synthesis of functionally and structurally diverse C_2 -symmetric NHPI analogues.

with methyl or phenyl chloroformate in the presence of Et_3N and a catalytic amount of DMAP. Allyl deprotection^[8] of the products then gave dicarbonates **6a** and **6b** (Table 1, entries 2 and 3). Similarly, diethers **7a** and **7b** (Table 1, entries 4 and 5), bis(silyl ether)s **8a** and **8b** (entries 6 and 7), and dicarbamates **9a–9e** (entries 8–12), were prepared readily.

Table 1: C_2 -symmetric NHPI analogues prepared according to Scheme 2.

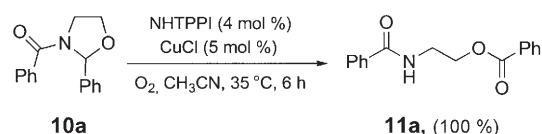
Entry	4 ^[a]	Electrophile	Catalyst ^[b]	Yield [%] ^[c]
1	4b	PhCOCl	5a R = Ph	80
2	4a	MeOCOCl	6a R = Me	78
3	4a	PhOCOCl	6b R = Ph	78
4	4b	$\text{CH}_2=\text{CHBr}$	7a R = $n\text{Pr}$ ^[d]	46
5	4b	$t\text{BuO}_2\text{CCH}_2\text{Br}$	7b R = $\text{CH}_2\text{CO}_2t\text{Bu}$	80
6	4b	TBDMSCl	8a SiR_3 = TBDMs	97
7	4b	TIPSCl	8b SiR_3 = TIPS	50
8	4b	PhNCO	9a R = Ph	84
9	4b	1-naphthyl-NCO	9b R = 1-naphthyl	31 (72) ^[e]
10	4a	BnNCO	9c R = Bn	68
11	4b	$\text{PhCH}(\text{NCO})\text{CH}_3$	9d R = $\text{CH}(\text{Ph})\text{CH}_3$	96
12	4a ^[f]	$\text{PhCH}(\text{NCO})\text{CH}_3$	9e R = $\text{CH}(\text{Ph})\text{CH}_3$	84

[a] Unless otherwise indicated, (*aS,aS*)-**4a** and (*aS,aS*)-**4b** were used.

[b] Deprotection method used for catalysts prepared from **4a**: sodium 2-ethylhexanoate (1.5 equiv), $[\text{Pd}(\text{PPh}_3)_4]$ (2 mol %), $\text{AcOEt}/\text{CH}_2\text{Cl}_2$ (1:2), RT; deprotection method used for catalysts prepared from **4b**: H_2 (atmospheric pressure), 10% Pd/C (0.25 g per mmol of **4b**), AcOEt , RT. [c] Unoptimized overall yield of the isolated pure catalyst. [d] Hydrogenation of the double bonds occurs during hydrogenolysis. [e] The yield based on recovered **4b** is given in brackets. [f] Compound (*aR,aR*)-**4a** was used. TBDMs = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

The aerobic oxidation of acetals to esters catalyzed by NHPI under mild conditions was reported recently.^[9] In particular, 1,3-dioxolanes are oxidized efficiently to ethylene glycol monoesters by ring opening. We discovered that an analogous oxidative ring opening occurs with *N*-acyl oxazolidines^[10] in the presence of NHPI-type catalysts: The aerobic oxidation of **10a**^[10b] as an 0.01 M solution in CH_3CN at 35 °C in the presence of catalytic amounts of *N*-hydroxy-3,4,5,6-tetraphenylphthalimide (NHTPPI)^[11] and CuCl gave **11a** in 100% yield (Scheme 3).

We found that chiral analogues of NHPI are also able to catalyze the oxidation of **10a** to **11a**. Interestingly, the partial oxidation of racemic **10a** with enantiopure catalysts occurs with kinetic resolution of the remaining **10a**. The efficiency of the kinetic resolution is highly dependent on the catalyst used (Table 2). When the reaction depicted in Scheme 3 was



Scheme 3. Oxidative ring opening of oxazolidine **10a** catalyzed by NHTPPI.

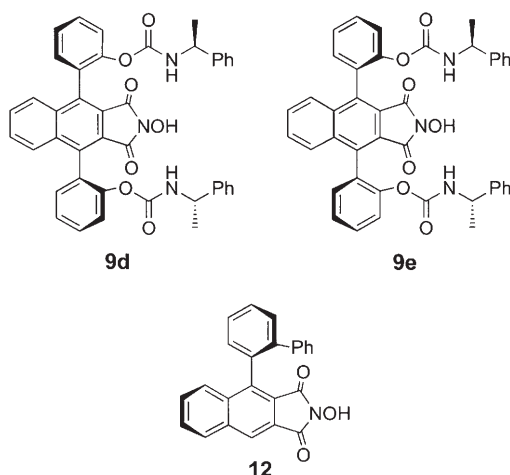
performed with catalyst **5a**, 52% conversion was observed after 24 h; the remaining **10a** had an *ee* value of 23%. These values correspond to a stereoselectivity factor $s^{[12]}$ of 1.9 (Table 2, entry 1). No significant improvements were observed with catalysts of type **6**, **7**, or **8** (Table 2, entries 2–7). The results obtained with carbamate-type catalysts were more remarkable: The use of catalyst **9a** led to 53% conversion and 50% *ee* for the remaining **10a**, which

Table 2: Oxidative kinetic resolution of oxazolidine **10a** catalyzed by enantiomerically pure NHPI analogues.^[a]

Entry	Catalyst	Conversion [%] ^[b]	<i>ee</i> [%] ^[c]	<i>s</i>
1	5a	52	23	1.9
2	6a	38	22	2.6
3	6b	37	20	2.4
4	7a	43.5	4	1.15
5	7b	75	28	1.5
6	8a	47	20	1.9
7	8b	64.5	30	1.8
8	9a	53	50	4.1
9	9b	25	22	6
10 ^[d]	9b	52	58	5.8
11 ^[d]	9c	50	65	9
12	9d	70	91	6.5
13	9d ^[d]	80	99	–
14	9e ^[d]	27	20 ^[e]	4
15	(–)- 12 ^[f]	75	28 ^[e]	1.5

[a] Reaction conditions, unless otherwise indicated: **10a** (0.01 M), catalyst (4 mol %), CuCl (5 mol %), CH_3CN , 35 °C, 24 h. [b] Determined by GC. [c] Determined by HPLC with a Chiralpak AS column. Unless otherwise indicated, the major remaining enantiomer of **10a** was the first enantiomer eluted. [d] A 0.1 M solution of **10a** in CH_3CN was used. [e] The major remaining enantiomer was the second enantiomer eluted. [f] The reaction was performed with 6 mol % of the catalyst.

corresponds to $s = 4.1$ (Table 2, entry 8). With catalyst **9b** only 25% conversion was observed, but with a stereoselectivity factor of 6. The conversion could be increased to 52% by using a 0.1M solution of **10a** while maintaining a similar s factor (Table 2, entries 9 and 10). A stereoselectivity factor of 9 was found for catalyst **9c**, but the conversion was limited to 50% (Table 2, entry 11). Catalyst **9d** combined high conversion with good selectivity: When the initial concentration of **10a** was 0.01M, 70% conversion occurred to leave **10a** with 91% ee ($s = 6.5$). A ten-fold increase in the substrate concentration resulted in 80% conversion and 99% ee (Table 2, entries 12 and 13). In contrast, much lower conversion was observed with the diastereomeric catalyst **9e**, along with a lower s factor (Table 2, entry 14). The use of the



first-generation catalyst (–)-**12**^[4] led to 75% conversion and 28% ee for the remaining **10a**, which corresponds to an s factor of only 1.5 (Table 2, entry 15). Optically active **10a** has not been described previously, nor has the absolute configuration of the individual enantiomers been reported. Accordingly, the major enantiomer remaining after kinetic resolution is indicated in Table 2 by reference to the elution order of the enantiomers on a Chiralpak AS HPLC column. When catalysts with stereogenic axes of configuration aS,aS were used (Table 2, entries 1–13), the major remaining enantiomer of **10a** was always eluted faster than the minor enantiomer. In the case of catalyst **9e**, which has the absolute configuration aR,aR , the major remaining enantiomer was eluted more slowly than the minor enantiomer. The absolute configuration of (–)-**12** is still unknown.

We next examined the oxidative kinetic resolution of a series of *N*-acyl oxazolidinones with catalyst **9d** (Table 3). The associated stereoselectivity factors of *N*-acetyl, *N*-pivaloyl, *N*-1-naphthoyl, and *N*-*p*-nitrobenzoyl analogues **10b**, **10c**, **10d**, and **10e** were significantly lower than that of the *N*-benzoyl derivative **10a** (Table 3, entries 1–5). The *p*-methoxybenzoyl derivative **10f** was oxidized rapidly and selectively: After 50 min the conversion was 52%, and the remaining **10f** had an ee value of 67%, with a corresponding stereoselectivity factor of about 9. After 1.2 h, 75% conversion had occurred, and 99% ee was observed for **10f**. When the amount of **9d**

Table 3: Oxidative kinetic resolution of various *N*-acyl oxazolidinones **10** catalyzed by **9d**.^[a]

Entry	Substrate	R	<i>t</i> [h]	Conv. [%] ^[b]	ee [%] ^[c]	s ^[d]
1	10a	Ph	24	80	99	6.5
2	10b	Me	16	50	25 ^[e]	2.1 ^[f]
3	10c	<i>t</i> Bu	4	50	26	2.2
4	10d	1-naphthyl	2	75	50	2.1
5	10e	<i>p</i> -NO ₂ C ₆ H ₄	24	50	45	4
6	10f	<i>p</i> -MeOC ₆ H ₄	0.8	52	67	8.7
7	10f	<i>p</i> -MeOC ₆ H ₄	1.2	75	99	–
8 ^[g]	10f	<i>p</i> -MeOC ₆ H ₄	2	52.5	70	9.1
9	10g	Me	1.5	43	36	4
10	10h	<i>i</i> Pr	1.2	59	80	8.2
11	10i	<i>t</i> Bu	1.5	76	76	4.9
12	10j	<i>o</i> -FC ₆ H ₄	1	51.6	84	21
13	10k	<i>o</i> -ClC ₆ H ₄	2	50.5	89	41
14	10l	<i>o</i> -BrC ₆ H ₄	3.2	40.5	60	24
15	10l	<i>o</i> -BrC ₆ H ₄	22	58	97	–
16	10m	<i>p</i> -BrC ₆ H ₄	0.6	67	90 ^[h]	7.3
17	10n	<i>o</i> -IC ₆ H ₄	2.3	39	60	> 50

[a] Reaction conditions, unless otherwise indicated: **10** (0.1 M), **9d** (4 mol%), CuCl (5 mol%), CH₃CN, 35°C. [b] The conversion was determined by NMR spectroscopy with triphenylmethane as a standard. [c] Unless otherwise indicated, the ee value was determined by HPLC with a Chiralpak AS column, and the major remaining enantiomer was the first enantiomer eluted. [d] For $s > 20$, the indicated values are an average of multiple experiments, whereas the corresponding values for conversion and ee are for a specific case. [e] The major remaining enantiomer was the second enantiomer eluted. [f] The reaction was performed at 20°C. [g] The reaction was performed with 1 mol% of **9d**. [h] The ee value was determined by HPLC with a Chiralcel OD-H column.

was reduced to 1 mol%, 52.5% conversion was observed after 2 h, and the remaining **10f** had an ee value of 70%, with no significant change in the s factor (Table 3, entries 6–8). *N*-*p*-Methoxybenzoyloxazolidinones **10g**, **10h**, and **10i**, with methyl, isopropyl, and *tert*-butyl substituents at the 2-position, respectively, were all oxidized at fast rates, and with stereoselectivity factors ranging from 4 to 8.2 (Table 3, entries 9–11). The oxidation rate of the *o*-fluorophenyl-oxazolidine **10j** was comparable to that of **10f**, but the associated s factor was much higher: After 1 h, the conversion was 51.6%, and the remaining **10j** had an ee value of 84%, which corresponds to an s factor close to 21 (Table 3, entry 12). An s factor of about 40 was found for the oxidation of its chlorinated analogue **10k**, with only a slight decrease in the reaction rate (Table 3, entry 13). The stereoselectivity factor associated with the *o*-bromophenyl analogue **10l** was close to 24. The remaining oxazolidine **10l** was obtained with 97% ee at 58% conversion (Table 3, entries 14 and 15). In contrast, the s factor of the *p*-bromophenyl analogue **10m** was only 7.3 (Table 3, entry 16). Finally, after 39% conversion of the *o*-iodophenyl-oxazolidine **10n** in the presence of **9d**, the remaining oxazolidine had an ee value of 60%, which corresponds to a stereoselectivity factor larger than 50

(Table 3, entry 17).^[13] To our knowledge, this is the highest reported *s* factor for a radical reaction.^[14] The absolute configuration was not known for any of the oxazolidines in the series **10b–n**. Enantiopure **10l** was obtained by recrystallization of a sample of the resolved compound with 97% *ee*. The oxazolidine stereogenic center was assigned the *R* configuration unambiguously by anomalous X-ray diffraction, which was made possible by the bromine atom.^[15] Thus, the *S* enantiomer of **10l** reacted faster than the *R* enantiomer when catalyst **9d** was used. Further studies are necessary to assign the absolute configuration of other resolved oxazolidines, but it is reasonable to anticipate similar behavior, at least for oxazolidines **10f**, **10j**, **10k**, **10m**, and **10n**.

In summary, we have reported the synthesis of readily variable, *C*₂-symmetric analogues of NHPI. These analogues exhibit catalytic activity in the oxidative ring opening of various *N*-acyl oxazolidines. The kinetic resolution of racemic oxazolidines is possible with enantiopure catalysts, with selectivity factors that are highly dependent on the substitution pattern of the catalyst. Fast reaction rates and selectivity factors larger than 20 were observed in some cases with the most efficient catalyst examined. Such catalysts could be of value for the synthesis of highly enantiomerically enriched oxazolidines.^[16] The resolved compounds **10k**, **10l**, and **10n** could be useful as synthetic intermediates, for example, in asymmetric cross-coupling reactions. However, the synthetic potential of enantiopure oxazolidines remains to be fully established. Oxazolidines also exhibit interesting biological properties: Several racemic oxazolidines have been reported to be insect repellents. It would be interesting to test the activities of individual enantiomers. Preliminary studies indicate that other types of substrates, such as silyl ethers of racemic secondary alcohols, are also oxidized by our new catalysts with kinetic resolution. The examination of these and further synthetic applications, as well as further improvement of the catalysts and mechanistic investigations, is currently under way.

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- [16] For experimental details of the synthesis of the catalysts and substrates, for experimental details of the asymmetric oxidation reactions, and for an ORTEP drawing of (*R*)-**10l**, see the Supporting Information.