CHEMISTRY
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Accepted Article

Title: Asymmetric Oxidative Cycloetherification of Naphtholic Alcohols

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201700667

Link to VoR: http://dx.doi.org/10.1002/chem.201700667

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10.1002/chem.201700667

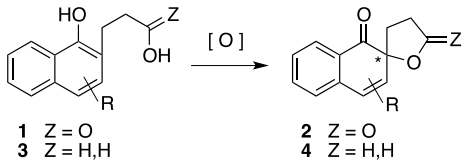
(Asymmetric Catalysis)

DOI: 10.1002/anie.200((will be filled in by the editorial staff))

Asymmetric Oxidative Cycloetherification of Naphtholic Alcohols**

*Nikita Jain, Sanjia Xu and Marco A. Ciufolini**

Significant efforts have been channelled in recent years toward the enantioselective oxidative cyclization of phenolic, and especially naphtholic, carboxylic acids (cf. **1** → **2**, Scheme 1). These reactions rely upon the use of chiral aryl iodide catalysts,[1] which are oxidized *in situ* to the *I*-hypervalent state, typically with MCPBA.[2] Noteworthy examples have been described by Kita,[3] Fujita,[4] and Uyanik and Ishihara.[5] Analogous reactions of non-carboxylic acid substrates appear to be unknown. For instance, the oxidative cyclization of alcohols **3** is documented only in the racemic series,[6] although a related bimolecular, enantioselective hydroxylation reaction has been developed by Quideau and Pouysegu.[7] Herein, we describe a catalytic, enantioselective variant of the process **3**→**4**.



Scheme 1. *Ortho*-oxidative cyclization of naphtholic substrates.

Uyanik-Ishihara iodides (Figure 1) are easily made and modified, and as such they are especially useful as starting points for the development of new transformations.[8] Initial forays thus focused

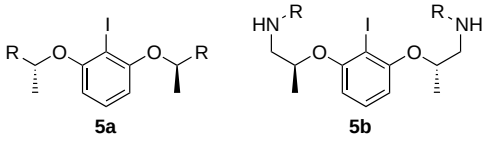
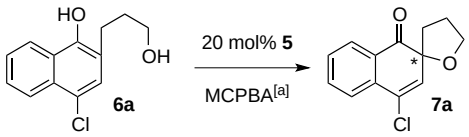


Figure 1. Structure the Uyanik-Ishihara chiral iodides, **5**.

on the oxidative cyclization of **3**, R=H, promoted by MCPBA and aryl iodides **5**, under conditions similar to those described in the literature for the cyclization of acids **1**. A potential challenge associated with the transformation **3** → **4** and related processes is that such reactions are acid-catalyzed, so that suppression of the carboxylic functionality may have an adverse effect on rates and yields. Indeed, alcohol **3**, R=H, reacted much more slowly than th corresponding acid. Furthermore, the reaction was best carried ou in the presence of 20 mol% of chiral iodide instead of the typical 1 mol%. Also, **3**, R=H, was a less-than-ideal substrate. Depending o conditions, nearly one-third of it was lost to oxidation to th corresponding 1,4-naphthoquinone; moreover, variable quantities c product **4**, R=H, underwent epoxidation of the double bond in th course of the reaction. No such problems were seen with **6a** (Tabl 1), which was thus used for subsequent work. As seen in Table 1 best results, in terms of rates and ee's, were achieved with iodide **5b** R = COMes (entry d): the same iodide of that type that also work best in the reaction **1** → **2**. However, yields remained in the mid-60

Table 1. Asymmetric cyclization of **6a** in the presence of catalysts **5**



entry	catalyst (R)	time (h)	% ee[b]	% yield[c]
a	**5a** (COOMe)[d]	42	13	27
b	**5a** (COOH)[d]	18	29	51
c	**5a** (CONH-Ar[1])[d],[e],[f]	32	65	62
d	**5b** (COAr[1])[d],[e]	15	90	65
e	**5b** (COAr[2])[e]	36	64	52
f	**5b** (COAr[3])[e]	33	74	60
g	**5b** (Ts)	37	27	46

[a] Conditions: 1.3 equiv MCPBA, –20 °C, 0.02 M in CH_2Cl_2. [b] Determined by chiral supercritical fluid chromatography (SFC). [c] After column chromatography. [d] Known compound: ref. 5. [e] Ar^1 = 2,4,6-$Me_3C_6H_2$; Ar^2 = 3,5-$(MeO)_2C_6H_3$; Ar^3 = 2,4,6-$(MeO)_3C_6H_2$. [f] Catalysts **5a** and **5b** promoted the opposite sense of induction.

Uyanik and Ishihara proposed that intramolecular H-bonding, a per Figure 2, may be a key aspect of catalyst operation.[5b] This led

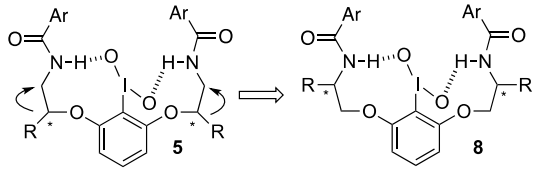


Figure 2. Working hypothesis for new catalyst design.

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[**] We gratefully acknowledge support for this research from the University of British Columbia, the Canada Research Chair program, and NSERC.

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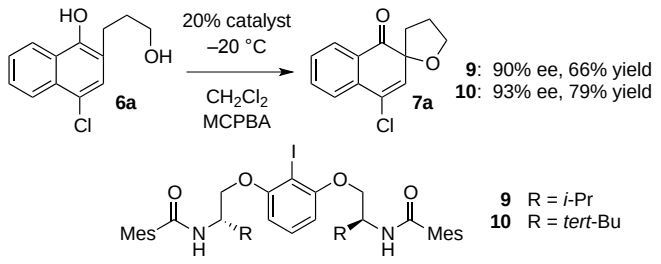
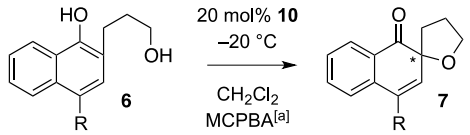
to the surmise that relocating the stereocenters closer to the amide NH group, as seen in **8**, might enforce the hydrogen-bonded conformation and improve catalyst efficiency. New iodides **9** and **10**[9] (Scheme 2) were thus evaluated. Catalyst **9** was equivalent to **5b**, R = COMes, (66% yield of **7a**, 90% ee). In contrast, iodide **10** afforded comparable ee's (93%), but yields were distinctly better (79%). Subsequent work thus focused on the use of **10**. An extensive survey of reaction conditions[10] confirmed that optimal results required operation in CH_2Cl_2 at –20 °C, with 20 mol % of **10** and 1.3 equiv of MCPBA. The rate of addition of MCPBA seemed to have no significant effect on overall efficiency; however, it was essential to avoid an excess of the reagent.



Scheme 2. Structure and performance of catalysts **9** and **10**.

Table 2 summarizes the results obtained in the cyclization of substrates **6** in the presence of **10** under optimized conditions. As far as asymmetric induction is concerned, substrates incorporating electron-withdrawing substituents produced generally better results

Table 2. Cyclization of alcohols **6** in the presence of catalyst **10**

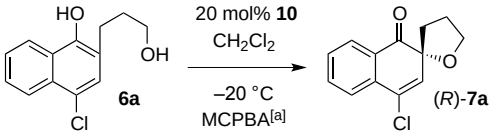


entry	R	time (h)	% ee[b]	% yield[c]
a	4-Cl	25	93[d]	79
b	4-Br	27	84	73
c	4-Me	20	76	29
d	4-C(O)Me	134	92	15
e	4-C(O)Ph	46	92	42[e]
f	4-C(O)(4-Tol)	55	92	41[f]
g	4-Ph	18	80	63[g]
h	4-(4-Tol)	38	75 (98)[h]	52
i	4-(3-MeO-C_6H_4)	41	69	73
j	4-(4-MeC(O)-C_6H_4)	21	88	75
k	4-(4-F-C_6H_4)	14	83 (90)[h]	64
l	4-(4-NC-C_6H_4)	38	92	71
m	4-(4-$MeSO_2$-C_6H_4)	13	90	78
n	4-(4-CF_3-C_6H_4)	39	90[d] (98)[h]	55
o	4-(3,5-$(CF_3)_2C_6H_3$)	35	93	47

[a] Conditions: 1.3 equiv MCPBA, –20 °C, substrate conc. = 0.02 M. [b] Determined by chiral SFC. [c] After column chromatography. [d] Absolute configuration was found to be *R* (see text). [e] 47% yield based on RSM. [f] 50% yield based on RSM. [g] 69% yield based on RSM. [h] ee of material remaining in the mother liquor after a single recrystallization.

that those exhibiting electron-donating ones. This may reflect a diminished tendency of the complex resulting upon the union of the substrate with the oxidized form of the catalyst to dissociate: an event that would erode ee's and induce various side reactions. An X-ray structural analysis of an appropriate derivative[9] of (+)-**7a** revealed that the spirocenter was of *R*-configuration. It should be noted that catalyst **5b**, R = COMes, afforded the opposite sense of induction, providing instead (*S*)-(–)-**7a**. An analogous X-ray structural study of a derivative[9] of (+)-**7n** also revealed this product to be of *R*-configuration.

Table 3. Cyclization of alcohol **6a** with recycled catalyst **10**

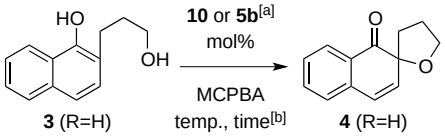


cycle	time (h)	% ee[b]	% yield[c]	% rec. cat.[c]
1[d]	25	93	79	96
2	29	93	74	90
3	27	92	77	95
4	27	92	78	93

[a] 1.3 equiv MCPBA, –20 °C, substrate conc. = 0.02 M. [b] By chiral SFC. [c] After column chromatography. [d] Fresh catalyst.

Iodide **10** is easily recovered from reaction mixtures by colum chromatography (> 90% yield), and it can be recycled with no los of efficacy. Results of typical experiments carried out with recycle **10** appear in Table 3. Further evaluation of **10** involved comparison with **5b**, R = COMes, in the cyclization of poo substrate **3**, R = H, to **4**, R = H, at various temperatures and catalys loadings. As far as optical induction goes, iodide **10** retaine efficacy even at rt and 5 mol% loading (Table 4), even though yield decreased appreciably at higher temperatures. This seems to provid support for the notion that repositioning the centers of chiralit closer to the H-bonding sites is beneficial for effective induction.

Table 4. Relative efficacy of iodidoarene catalysts **10** and **5b** (R = mesitoyl) in the cyclization of **3**, R = H, to **4**, R = H.



mol%	T (°C)	time (h) **10** (**5b**)	% ee **10** (**5b**)[c]	% yield of **4** **10** (**5b**)[d]
20	–20	21 (12)	93 (93)	67 (61)
20	rt	3.5 (2.5)	93 (86)	45 (43)
10	–20	20.5 (16)	96 (90)	50 (46)
10	0	9.0 (5.5)	93 (89)	46 (42)
10	rt	6.5 (4.5)	92 (86)	41 (30)
5	rt	8.5 (7.0)	89 (82)	35 (23)

[a] R = 2,4,6-$Me_3C_6H_2C(O)$. [b] Conditions: CH_2Cl_2, 1.3 equiv MCPBA, –20 °C, substrate conc. = 0.02 M,. [c] Determined by chiral SFC. [d] After column chromatography.

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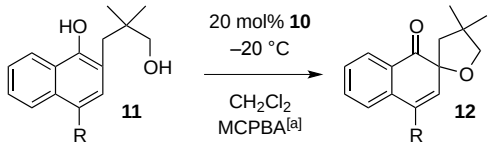
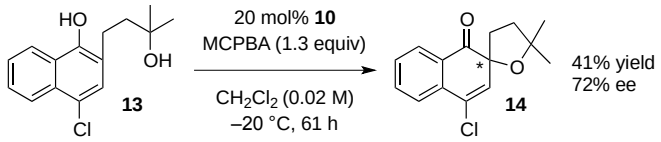
Table 5. Oxidative cyclization of substrates **11** mediated by **10**.



entry	R	time (h)	% ee[b]	% yield[c]
a	H	70	98	61
b	Cl	60	76	66
c[d]	Br	36	74	77
d[d]	4-Ph	36	90	50
e[d]	4-(4-CF_3-C_6H_4)	36	87	64

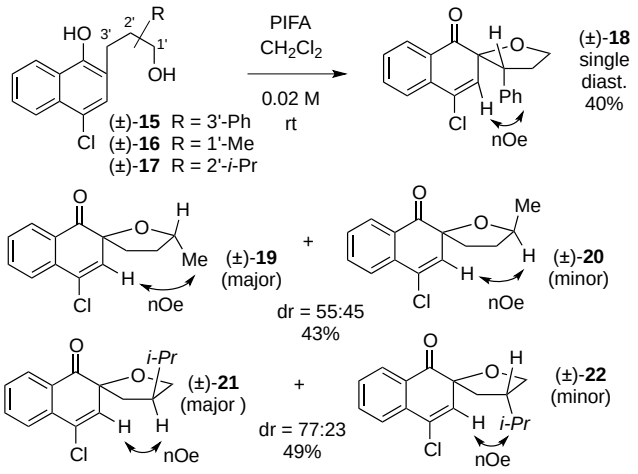
[a] 1.3 equiv MCPBA, –20 °C, substrate conc. = 0.02 M. [b] Determined by chiral SFC. [c] After column chromatography. [d] 1.8 equiv of MCPBA was used.

A drawback of above processes is that reaction times are long. In an effort to shorten reaction times, we examined the cyclization of substrates **11** (Table 5), wherein the Thorpe-Ingold effect[11] of the gem-dimethyl arrangement could promote a rate acceleration. Contrary to this expectation, slower reaction rates were observed both with compounds **11** as well as with naphthol **13** (Scheme 3), which also afforded lower optical and chemical yield relative to **11b**.



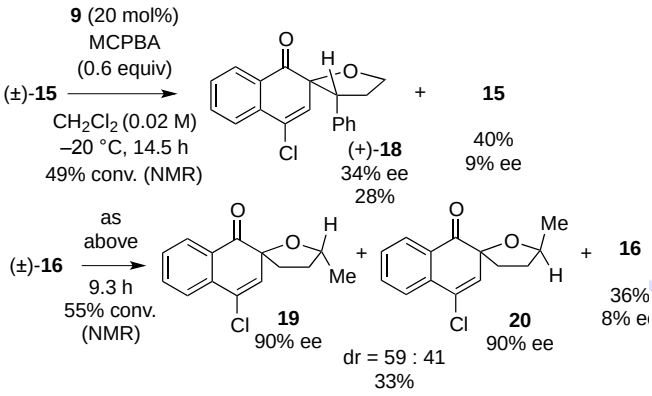
Scheme 3. Oxidative cyclization of **13** mediated by catalyst **10**.

These results suggest that unfavorable steric interactions within the substrate-catalyst complex override the Thorpe-Ingold effect. However, they also raise the question of whether one could harness such interactions to influence the diastereoselectivity of the cyclization of naphthols carrying a single substituent on the hydoxypropyl chain, or even to induce kinetic resolution. The latter issues were addressed with (±)-**15**-**17**, which upon oxidative cyclization with PIFA in CH_2Cl_2 afforded the expected racemic products in 40-50% yield (Scheme 4). Product (±)-**18** emerged as a single diastereomer, the NOESY-2D spectrum of which was clearly in accord with the configuration shown. The reaction of (±)-**16** was almost non-selective, while that of (±)-**17** exhibited moderate selectivity (77:23) in favor of (±)-**21**. Individual product isomers proved difficult to separate by standard chromatography.[12] The relative configuration of each isomeric pair was thus assigned based on a NOESY-2D study of the mixture (after purification).[9]



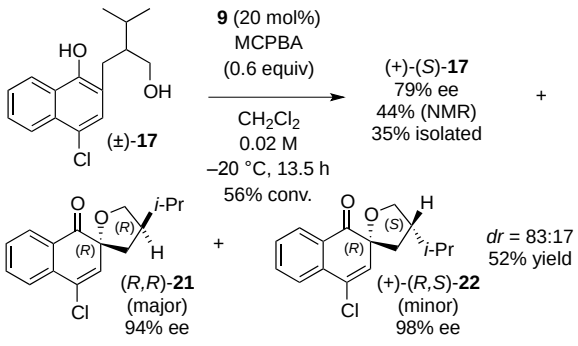
Scheme 4. Diastereoselective oxidative cyclization of (±)-**15**-**17**.

The enantioselective variant of the process was studied with both iodides **9** and **10**. These proved to be equally efficient in terms of optical and chemical yields, but rates were 5 times faster with **9**, which therefore was the catalyst of choice in this case. Reactions were run to about 50% conversion in order to evaluate the efficienc of kinetic resolution. As seen in Scheme 5, oxidative cyclizatio mediated by **9** proceeded with virtually unchanged levels c diastereoselectivity, indicating that the chiral catalyst has only minor influence on that aspect of the reaction. The cyclization c (±)-**15** proceeded with poor chemical (28%) and optical (34% ee yields; also, recovered **15** (40%) was of only 9% ee. The sam reaction of (±)-**16** was highly enantioselective (90% ee for eac diastereomer), but diasteroselectivity, chemical yields, and optica enrichment of unreacted alcohol were unsatisfactory. The absolut configurations of the various products were not determined.



Scheme 5. Enantioselective oxidative cyclization of *rac*-**15** and **16**.

The behavior of (±)-**17** (Scheme 6) was more interesting. As i the previous cases, diastereoselectivity was almost unaffected (83:1 vs. 77:23), but yields were higher (52%), ee's were excellent (94% for the major diastereomer, (*R*,*R*)-**21**; 98% for the minor one, (*R*,*S*) **22**), and recovered alcohol (+)-(*S*)-**17** was enriched to 79% ee.



Scheme 6. Oxidative cyclization of (±)-**17** mediated by catalyst **9**.

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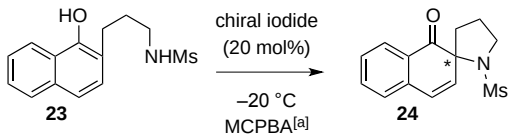
The absolute configuration of these materials was determined as follows. Recovered (+)-**17** of 79% ee was used in a second round of oxidative cyclization mediated by **9** run to 43% conversion. This operation returned residual (+)-**17** of 96% ee. An X-ray study of a derivative[9] revealed that the compound was of (*S*)-configuration; therefore, (*R*)-(–)-**17** is the fast-reacting enantiomer. This implies that the absolute configuration of enantioenriched **21** is (*R*,*R*), as shown. Oxidative cyclization of (+)-**17** of 96% ee in the presence of **9** afforded (+)-**22** of 99% ee. This product was identical to the major enantiomer of the minor diastereomer produced in the first experiment. Therefore, the configuration of the carbon atom bearing the *i*-Pr group in (+)-**22** is (*S*), and that of the spirocenter must be (*R*). This is consistent with the sense of enantioinduction observed with simpler substrates.

A preliminary picture of the preferences of catalysts **9**-**10** thus emerges as follows. The iodides have an insignificant effect on diastereoselectivity, which remains largely under substrate control. Kinetic resolution of the substrate is possible with alcohols of the type **17**, wherein a substituent is present at C-2'. These compounds react with fair diastereoselectivity and excellent optical induction. The sense of enantioinduction of the catalyst is unaffected by the presence of the C-2' substituent.

On a final note, iodide **10** was briefly evaluated in the enantioselective oxidative cyclization of a naphtholic sulfonamide: another undocumented process[13] that appears to be even more problematic than the analogous reaction of alcohols **3**. So far as optical induction is concerned, iodide **10** appears to be advantageous relative to **5b**, R = mesitoyl, in the oxidative cyclization of **23** (Table 6). An X-ray analysis of material recrystallized to 96% ee revealed that (+)-**24** obtained with **10** was of *R*-configuration, while (–)-**24** obtained with **5b**, R = mesitoyl, was of *S*-configuration.[9]

Table 6. Relative efficacy of iodides **10** and **5b**, R = MesCO, in the cyclization of sulfonamide **23**



23 **24**

entry	iodide	selectivity	% ee[b]	% yield[c]
a	**5b**[d]	(–)-(*S*)-**24**	46	20
b	**10**	(+)-(*R*)-**24**	67	20

[a] Conditions: 20 mol% chiral iodide, 1.3 equiv MCPBA, –20 °C, CH_2Cl_2, substrate conc. = 0.02 M, 10-15h. [b] Determined by chiral HPLC. [c] After column chromatography. [d] R = MesCO.

In summary, the enantioselective oxidative cyclization of non-carboxylic naphtholic substrates, such as alcohols **3**, **6**, **11**, **13** appears to be best carried out with chiral iodide **10**, while that of alcohol **17** is best achieved with chiral iodide **9**. Compounds **9**-**10** embody a structural modification of the Uyanik-Ishihara iodide **5b**. The new catalyst design may also be beneficial for the enantioselective oxidative cyclization of naphtholic sulfonamides such as **23**. Additional efforts in this area are ongoing and pertinent results will be described in due course.

Received: ((will be filled in by the editorial staff))
Published online on ((will be filled in by the editorial staff))

Keywords: asymmetric cycloetherification, asymmetric catalysis, hypervalent iodine, oxidative amidation, phenols

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[9] See Supporting Information for details.

[10] Details will be provided in a forthcoming full paper.

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[12] In contrast, excellent separation was attained by SFC (Supporting Information).

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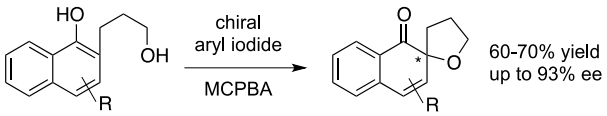
Layout 2:

(Asymmetric Catalysis)

Nikita Jain, Sanjia Xu, Marco A. Ciufolini* _____ **Page – Page**

Asymmetric Oxidative Cycloetherification of Naphtholic Alcohols



A catalytic, enantioselective oxidative cycloetherification reaction olic alcohols is described.