Catalytic, Asymmetric, Bromine-Induced Semipinacol Rearrangements at Unactivated Double Bonds

Christian H. Müller, Michael Wilking, Ansgar Rühlmann, Birgit Wibbeling, Ulrich Hennecke*

Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstraße 40, 48149 Münster, Germany
Fax +49(251)8336523; E-mail: ulrich.hennecke@uni-muenster.de

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Abstract: A new catalyst system for the enantioselective bromine-induced semipinacol rearrangement of cyclic allylic alcohols is described. Using the commercially available $(DHQD)_2Pyr$ catalyst the products containing an all-carbon quaternary chiral centre can be obtained in good yield and high enantioselectivity.

Key words: asymmetric catalysis, bromine, electrophilic addition, halogenation, rearrangement

Intramolecular rearrangements like the pinacol, semipinacol, and related rearrangements are useful reactions for the construction of sterically congested carbon frameworks.[1] Such rearrangements under 1,2-migration are generally stereospecific and well suited for the construction of quaternary carbon centres. In many cases, these reactions are also diastereoselective, and the stereochemical outcome of the reactions is determined by preexisting stereocentres (substrate control).[1] However, reagent-controlled semipinacol-type rearrangements are much more difficult to achieve, and up to now only a few examples describing catalytic, enantioselective versions have appeared. Almost all of them use activated double bonds such as allenes or enol ethers. This includes metal-catalysed ring-expansion reactions of allyl carbonates, allenes and alkynes,[2] organocatalytic ring expansions at α,β-unsaturated double bonds,[3] and Brønsted acid catalysed (semi-) pinacol rearrangements of enol ethers and indoles.[4] Highly enantioselective semipinacol rearrangements at simple nonactivated alkenes are more challenging, require more reactive electrophiles, and have not been reported up to now. Halogen electrophiles are well-known to induce semipinacol rearrangements at simple alkenes[5] and halogen-induced semipinacol rearrangements proved to be very useful in natural product synthesis.[6] We speculated that an enantioselective version of this reaction should be feasible considering the recent progress made on enantioselective halocyclisation reactions and related enantioselective halogen additions to double bonds.[7–9] Furthermore, initial studies on stoichiometric fluorine-induced asymmetric semipinacol rearrangements by Tu showed that moderate to good enantioselectivities can be achieved for these reactions.[10] During the preparation of this manuscript two publications by the same group appeared showing highly enantioselective, catalytic bromine-induced semipinacol rearrangements at activated double bonds (cyclic enol ethers)[11] and, for the first time, at nonactivated acyclic alkenes.[12] In parallel, we now show for the first time catalytic, bromine-induced, enantioselective semipinacol rearrangements of cyclic alkenes.

To test our hypothesis we chose cyclic allyl alcohol **1a**, easily available by addition of phenyllithium to commercially available methylcyclohexenyl-1-carboxylate, as our model compound. Upon treatment with NBS in dichloromethane, **1a** rearranges under 1,2-migration of a phenyl group to give racemic 2-bromocyclohexane derivative **2a** containing an all-carbon quaternary chiral centre whose structure was verified by NMR and X-ray crystallography.[13] In initial attempts to induce enantioselectivity, a range of catalysts that have been previously employed in enantioselective halogenation reactions were screened (Figure 1).

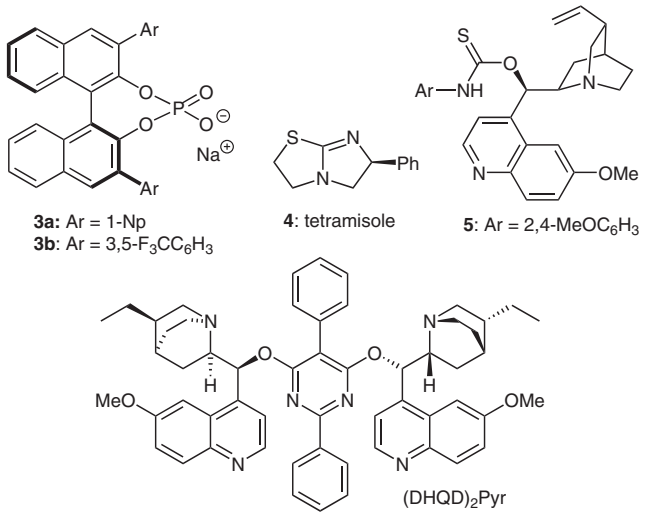

Figure 1 Catalysts employed in screening

Under typical reaction conditions (20 mol% catalyst, 1.2 equiv NBS), most catalysts led to full conversion but provided **2a** with a low enantiomeric excess. For example, the application of BINOL-derived phosphoric acid sodium salts **3a** and **3b** (Figure 1), previously employed in bromoetherification reactions[9d] gave only 5% and 6% ee (Table 1, entry 1, 2). A quinine-derived thiocarbamate **5** (Figure 1),[8d] previously established as highly enantioselective catalyst for bromolactonisations, afforded only racemic product, while tetramisole **4** (Figure 1) – a

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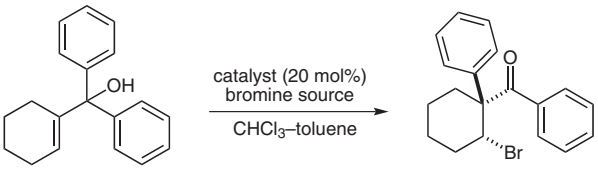
nucleophilic acylation catalyst[14] – led to 6% ee. More fruitful was the application of dimeric cinchona alkaloid catalysts known from the Sharpless asymmetric dihydroxylation[15] and previously employed for halogenation reactions by Borhan[8b] and Nicolaou.[9g] Using 20 mol% of $(DHQD)_2AQN$, $(DHQD)_2PHAL$, or $(DHQD)_2Pyr$ (Figure 1) enantioselectivities of 5%, 23%, or 71% ee could be achieved (Table 1, entries 5–7). This screening established $(DHQD)_2Pyr$ clearly as catalyst of choice. Further optimisation of the reaction conditions showed the reaction to be highly dependent on the bromine source. The application of the more reactive 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) led to only 5% ee, whereas less reactive bromine sources like *N*-bromo-2-pyrrolidinone (NBPyr) or *N*-bromoacetamide (NBAc) were far superior (84% and 89% ee, respectively, Table 1, entries 8–10). The solvent mixture of chloroform–toluene (50:50) proved to be optimal as the reaction in pure chloroform provided almost racemic product, and in pure toluene only a very low conversion (<5%, while the enantioselectivity was high, 92% ee) was achieved.[16] Interesting observations were made by using additives in this reaction. Acidic additives such as benzoic acid or *N*-Boc-L-phenyl glycine were necessary in previous haloge-

Table 1 Catalyst Screening and Optimisation of Reaction Conditions



1a **2a**

Entry	Catalyst	Bromine source	Solvent ($CHCl_3$–toluene)[b]	Temp (°C)	ee (%)
1	**3a**	NBS	50:50	–78 to r.t.	5
2	**3b**	NBS	50:50	–78 to r.t.	6
3	**4**	NBS	50:50	–78 to r.t.	rac.
4	**5**	NBS	50:50	–78 to r.t.	6
5	$(DHQD)_2AQN$	NBS	50:50	–78 to r.t.	5
6	$(DHQD)_2PHAL$	NBS	50:50	–78 to r.t.	23
7	$(DHQD)_2Pyr$	NBS	50:50	–78 to r.t.	71
8	$(DHQD)_2Pyr$	NBPyr[a]	50:50	–78 to r.t.	84
9	$(DHQD)_2Pyr$	DBDMH[a]	50:50	–78 to r.t.	7
10	$(DHQD)_2Pyr$	NBAc[a]	50:50	–10	89
11	$(DHQD)_2Pyr$	NBS	100:0	–20	rac.
12	$(DHQD)_2Pyr$	NBS	0:100	–20	92[c]
13	$(DHQD)_2Pyr$	NBS	50:50	0	38
14	$(DHQD)_2Pyr$	NBAc	50:50	–10	0[d]
15	$(DHQD)_2Pyr$	NBAc	50:50	–10	36[e]
16	$(DHQD)_2Pyr$	NBAc	50:50	–10	87[f]
17	$(DHQD)_2Pyr$	NBAc	50:50	–10	90[g]
18	$(DHQD)_2Pyr$	DCDMH[a]	50:50	0	45
19	$(DHQD)_2Pyr$	NIS	50:50	0	5

[a] The halogen sources were: *N*-bromo-2-pyrrolidinone (NBPyr), 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), *N*-bromoacetamide (NBAc), 1,3-dichloro-5,5-dimethylhydantoin (DCDMH).
[b] A $CHCl_3$–toluene solvent mixture was used, the table shows the ratios used.
[c] The conversion was below 5% after 3 d.
[d] 20 mol% benzoic acid used as additive.
[e] 10 mol% *N*-Boc-L-phenyl glycine used as additive.
[f] 5 mol% catalyst.
[g] 5 mol% catalyst and 10 mol% Na_2CO_3.

nations using dimeric cinchona alkaloid catalysts to achieve high enantioselectivities.[8b,11] In our case, these additives turned out to be detrimental to the enantioselectivity, leading even to racemic product if benzoic acid was used (Table 1, entries 14 and 15). On the other hand, small amounts of a base such as sodium carbonate led to a slight improvement in enantioselectivity and allowed the lowering of the catalyst loading to 5 mol% without a significant loss of enantioselectivity (Table 1, entries 16 and 17). Attempts to use other halogens (chlorine, iodine) were not successful (Table 1, entries 18 and 19). Under the optimised reaction conditions [$(DHQD)_2Pyr$ (5 mol%), Na_2CO_3 (10 mol%), NBAc (1.2 equiv), –10 °C, 72 h] the product **2a** could be obtained in 78% isolated yield and with 90% ee. The product **2a** is highly crystalline and its crystal structure could be determined, establishing the absolute configuration of the major enantiomer as [(1*S*),(2*R*)-2-bromo-1-phenyl-cyclohexyl](phenyl)methanone (Figure 2).

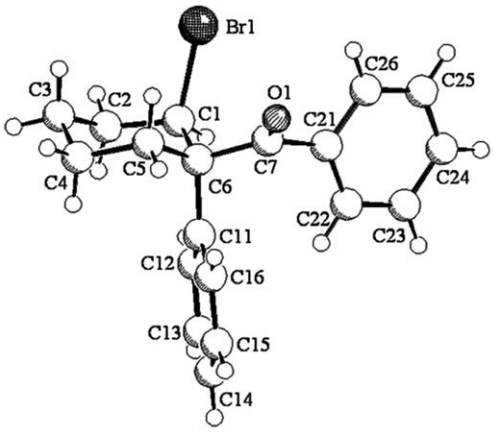
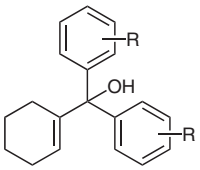
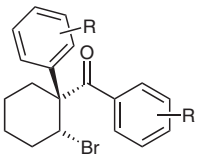
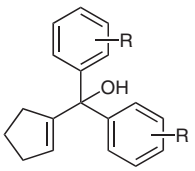
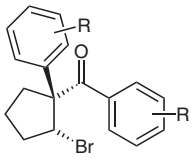


Figure 2 Crystal structure of compound **2a**

The optimised reaction conditions were used to rearrange a variety of different starting materials (Table 2). Cyclohexane derivatives with electron-rich migrating phenyl groups usually behaved very well and gave the desired product in good yields and with enantioselectivities from 76% to 90% ee (Table 2, entries 1, 4, 6, and 7). If the phenyl ring contained an electron-withdrawing group like chlorine or fluorine, reactions became much slower and required higher reaction temperatures and/or longer reaction times to reach full conversion (Table 2, entries 3 and 5). However, enantioselectivities were still good (76–84% ee). With a chlorine group in the *ortho* position the reac-

Table 2 Substrate Scope[a]

Entry	Substrate	Temp (°C)	Time (h)	Product	Isolated yield (%)	ee (%)
						
1	**1a** R = H	–10	72	**2a**	78	90
2	**1a** R = H	–10	72	*ent*-**2a**	55	78[b]
3	**1b** R = 4-Cl	–5	100	**2b**	44	76
4	**1c** R = 4-Me	–15	48	**2c**	69	81
5	**1d** R = 4-F	–5	100	**2d**	69	84
6	**1e** R = 4-OMe	–15	48	**2e**	91	76
7	**1f** R = 3-OMe	–15	48	**2f**	43	90
8	**1g** R = 2-Cl	r.t.	42	**2g**	24	52
						
9	**1h** R = H	–5	72	**2h**	43	37
10	**1i** R = 4-OMe	0	72	**2i**	52	40
11	**1j** R = 4-F	r.t.	100	**2j**	–	–

[a] Reaction conditions: 5 mol% $(DHQD)_2Pyr$, Na_2CO_3 (10 mol%), NBAc (1.2 equiv), $CHCl_3$–toluene (50:50).
[b] The pseudoenantiomeric $(DHQ)_2Pyr$ was used instead of $(DHQD)_2Pyr$.

tion became even slower and yield and enantioselectivity dropped significantly (24%, 52% ee, Table 2, entry 8). The cyclopentene derivatives proved to be in general much less reactive compared to the cyclohexanes (Table 2, entries 9–11). Even with the electron-rich migrating phenyl groups higher reaction temperatures had to be used. The enantioselectivities were also not as good as those obtained for the cyclohexane derivatives (37–40% ee). If the migrating aryl group contained an electron-withdrawing group such as fluorine no rearrangement could be observed and heating to elevated temperatures led only to decomposition of the starting material. The lower reactivity of the cyclopentenes compared to the cyclohexenes is puzzling, but has been observed before in related semipinacol rearrangements of cyclohexene and cyclopentene epoxides.[17]

In summary, we present a new enantioselective catalyst system for bromine-induced semipinacol rearrangements at nonactivated double bonds in cyclic systems. Under the optimised reaction conditions using the commercially available $(DHQD)_2Pyr$ catalyst the products containing all-carbon quaternary chiral centres are available in good yields and good enantioselectivities.

Typical Experimental Procedure for the Enantioselective Bromination–Semipinacol Rearrangement

Compound **1a** (79.2 mg, 0.30 mmol), $(DHQD)_2Pyr$ (13.2 mg, 0.015 mmol), and Na_2CO_3 (3.2 mg, 0.03 mmol) were placed in an argon-filled Schlenk flask with a rubber septum. Toluene (3 mL) and $CHCl_3$ (3 mL) were added, and the mixture was cooled to –10 °C. Recrystallised *N*-bromoacetamide (49.7 mg, 0.36 mmol) was added, and the reaction mixture was stirred at –10 °C until full conversion was reached (TLC control). Sat. $Na_2S_2O_3$ solution (5 mL) was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried over $MgSO_4$, the solvent was evaporated, and the crude product was purified by flash chromatography to provide the product **2a** (80 mg, 0.23 mmol, 78%, 90% ee) as a white crystalline solid.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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