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Catalytic Enantioselective [2,3]-Rearrangements of Amine *N*-Oxides

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Supporting Information

ABSTRACT: The first Pd-catalyzed enantioselective [2,3]-rearrangement of allylic amine *N*-oxides is described, which formally represents an asymmetric Meisenheimer rearrangement. The mild reaction conditions enable the synthesis of chiral nonracemic aliphatic allylic alcohol derivatives with reactive functional groups. On the basis of preliminary studies, a cyclization-mediated mechanism is proposed.

[2,3]-Sigmatropic rearrangements of ammonium zwitterions are powerful transformations for the synthesis of chiral molecules.[1] Despite the importance of these reactions, examples of enantioselective catalysis are rare. For example, there have been no reports of a catalytic and enantioselective [2,3]-Meisenheimer rearrangement of allylic amine *N*-oxides since its initial discovery over 90 years ago (Scheme 1).[2] The earliest asymmetric variants of the Meisenheimer rearrangement employed chiral auxiliaries on nitrogen (R^1 and R^2) to guide the stereoselectivity in the newly formed carbon stereocenter.[3,4] We were interested in developing a catalytic enantioselective process, wherein a chiral catalyst would govern the formation of enantioenriched chiral hydroxylamine products. In this communication we describe our efforts to realize the first catalytic enantioselective [2,3]-rearrangement of allylic amine *N*-oxides.

Our first goal was to establish a platform for metal-catalyzed amine *N*-oxide [2,3]-rearrangements. There are no general strategies to accelerate these types of transformations in a manner that is amenable to asymmetric catalysis, presumably because the reactive substrates usually rearrange thermally in the absence of catalyst. We initiated our studies with achiral *N*-oxide **2**, which was synthesized from dibenzyl allyl amine and purified by column chromatography. We found that it was relatively stable to thermal rearrangement at −20 °C (Table 1, entry 1). Although we did not observe any rearranged product in the presence of several metal catalysts (e.g., entries 2−5), we discovered that $Pd(OAc)_2$ catalyzed the [2,3]-rearrangement in good yield (entry 6).

On the basis of the ability of achiral $Pd(OAc)_2$ to accelerate the [2,3]-rearrangement of amine *N*-oxide **2**, *we hypothesized that chiral Pd(II) salts may be able to catalyze the enantioselective rearrangement*. A representative sample of phosphoramidites is described in Table 1 (entries 7−14).[5] We observed moderate levels of enantiomeric excess with phosphoramidite ligand **4a**. The relative stereochemistry of the ligands had a profound impact on enantioselection. For example, phosphoramidite **5** (the diastereomer of ligand **4a**) produced racemic hydroxylamine product (entry 8). Steric bulk at the 3- and 3′-positions of the BINOL backbone also affected the enantioselectivity of the rearrangement (entry 7 vs entries 9−11). Eventually, we discovered the positive influence of electron-withdrawing groups in the enantioselectivity of the transformation. For example, an ortho-CF_3 group on the 3- and 3′-phenyl substituents (**4e**) led to an increase of 17% in enantiomeric excess (entry 9 vs 12). Encouraged by this observation, we synthesized the CF_3 substituted ligand **4f**,

Scheme 1

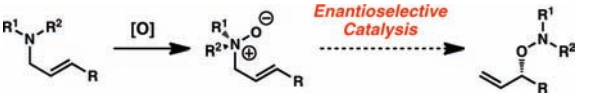
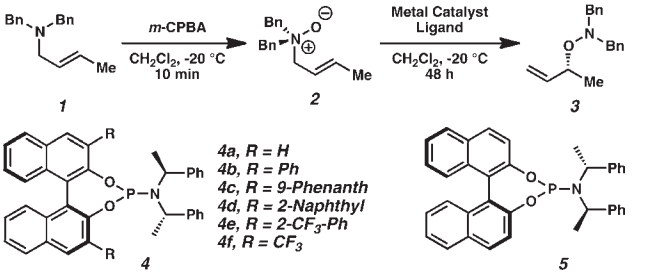


Table 1. Optimization of Reaction Conditions



entry	metal catalyst[a]	ligand[b]	yield (%)[c]	ee (%)
1	–	–	< 5	–
2	$NiCl_2(PPh_3)_2$	–	0	–
3	$[Rh(COD)Cl]_2$	–	6	–
4	$Cu(OTf)_2$	–	0	–
5	$Pd(PPh_3)_4$	–	0	–
6	$Pd(OAc)_2$	–	96	–
7	$Pd(OAc)_2$	**4a**	68	18
8	$Pd(OAc)_2$	**5**	76	0
9	$Pd(OAc)_2$	**4b**	64	30
10	$Pd(OAc)_2$	**4c**	63	38
11	$Pd(OAc)_2$	**4d**	80	46
12	$Pd(OAc)_2$	**4e**	56	47
13	$Pd(OAc)_2$	**4f**	82	85
14[d]	$Pd(OAc)_2$	**4f**	81	93

[a] 10 mol % metal catalyst. [b] 24 mol % ligand. [c] Isolated yield. [d] 20 mol % MeOH and 10 mol % *m*-chlorobenzoic acid were added.

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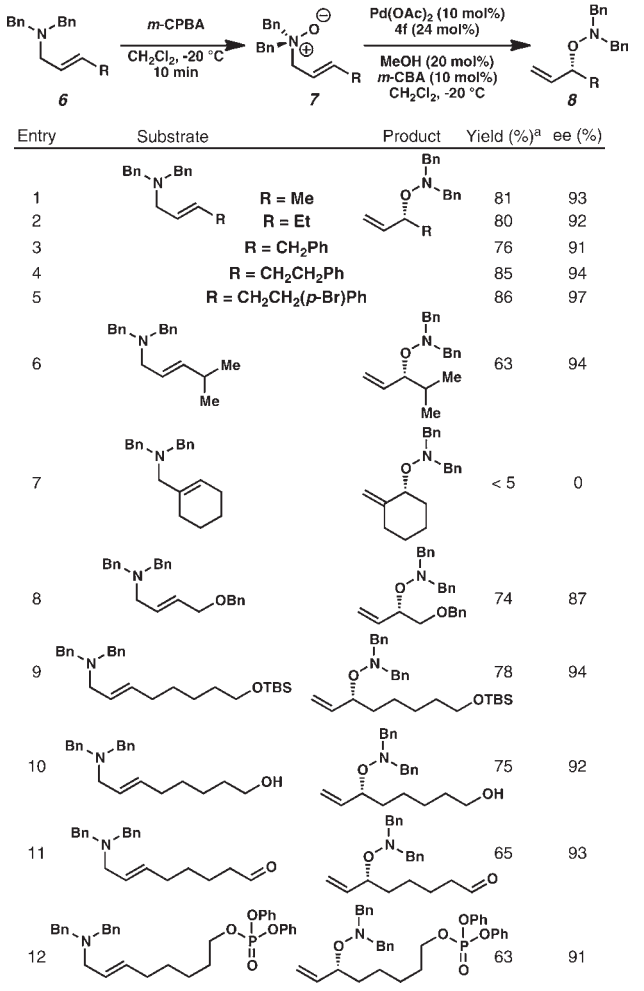
Table 2. Substrate Scope of the Enantioselective [2,3]-Rearrangement

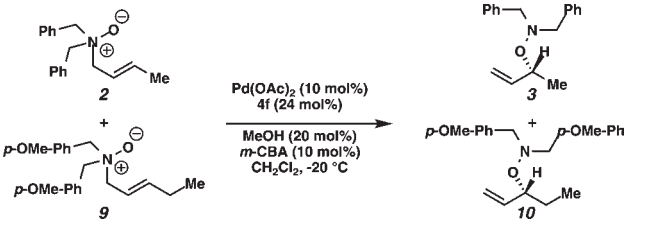


[a] Isolated yield.

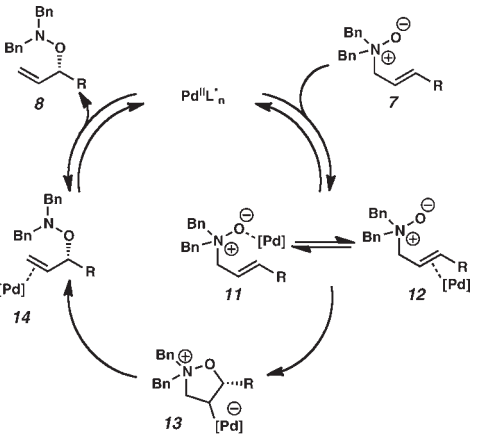
which provided the desired product in high yield and enantioselectivity (entry 13).[6] An examination of reaction conditions revealed the superiority of CH_2Cl_2 as a solvent for this rearrangement. Interestingly, the presence of 20 mol % MeOH and 10 mol % *meta*-chlorobenzoic acid (*m*-CBA) led to slightly elevated enantioselectivity (entry 14).[7]

With the optimized reaction conditions in hand, we explored the substrate scope of the enantioselective [2,3]-rearrangement of amine *N*-oxides (Table 2). The reaction tolerated a series of alkyl substituents at C3 of the allylic system, which furnished aliphatic allylic alcohol derivatives in good yields and enantioselectivities (entries 1−4). Substrates that contain aryl bromides (entry 5) and heteroatoms (entries 8 and 9) also behaved well in this transformation. Allylic hydroxylamines with branched side chains were produced in diminished yield but in high enantiomeric excess (entry 6). Due to the mildness of the reaction conditions, we were also able to synthesize chiral allylic hydroxylamine products with reactive functional groups that are incompatible with many known methods for the synthesis of chiral alcohol derivatives.[8−11] For example, free alcohols, aldehydes, and phosphate esters were well tolerated (entries 10−12). Unfortunately, a substrate with branching at the C2 position was not reactive under our optimized reactions conditions (entry 7), which supports our proposed mechanism for this process (vide infra).[12] The absolute stereochemistry of several hydroxylamine products was determined by facile N−O bond cleavage and chemical correlation to known compounds.[13]

Scheme 2



Scheme 3



To gain insight into the mechanism of this enantioselective process, we conducted a crossover experiment with amine *N*-oxides **2** and **9** (Scheme 2). The exclusive formation of hydroxylamines **3** and **10**, in conjunction with the low reactivity of Pd(0) catalysts (Table 1, entry 5), suggests the absence of an allylpalladium intermediate or intermolecular attack of an oxygen nucleophile, which are evoked in other metal-catalyzed rearrangements.[14]

In light of our initial data, we propose a mechanism for this enantioselective process wherein the Pd(II)-phosphoramidite catalyst acts as a chiral π-acid to activate the amine *N*-oxide substrate in a manner that is analogous to Overman's enantioselective rearrangement of allylic trichloroacetimidates (Scheme 3).[15] While it is not clear whether the reactive species is oxide-bound complex **11** or olefin-bound complex **12**, we surmise that heterocycle **13** is formed. This cyclization-mediated mechanism is consistent with the poor reactivity of C2-substituted substrates (Table 2, entry 7), which cannot form a heterocyclic intermediate with a sterically hindered fully substituted carbon bonded to Pd. Subsequent Grob-type fragmentation reveals Pd-bound hydroxylamine **14**.

In conclusion, we have developed the first catalytic enantioselective [2,3]-rearrangement of allylic amine *N*-oxides, which represents a formal asymmetric Meisenheimer rearrangement. The mild reaction conditions enable the generation of chiral hydroxylamines with traditionally reactive functional groups that may be difficult to access with known protocols for the synthesis of chiral alcohol derivatives. The N−O bond in the rearrangement products can be easily cleaved to unveil chiral secondary

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alcohols. A more detailed study of the mechanism of this enantioselective process and its application to the synthesis of complex natural products are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Attempts to lower the loading of $Pd(OAc)_2$ and ligand **4f** led to prolonged reaction times and diminished enantioselectivities, presumably because of the competing uncatalyzed background reaction.

(7) Currently, we do not understand the role of MeOH and *m*-CBA in this transformation.

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