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Stereospecific Asymmetric Synthesis of Tertiary Allylic Alcohol Derivatives by Catalytic [2,3]-Meisenheimer Rearrangements

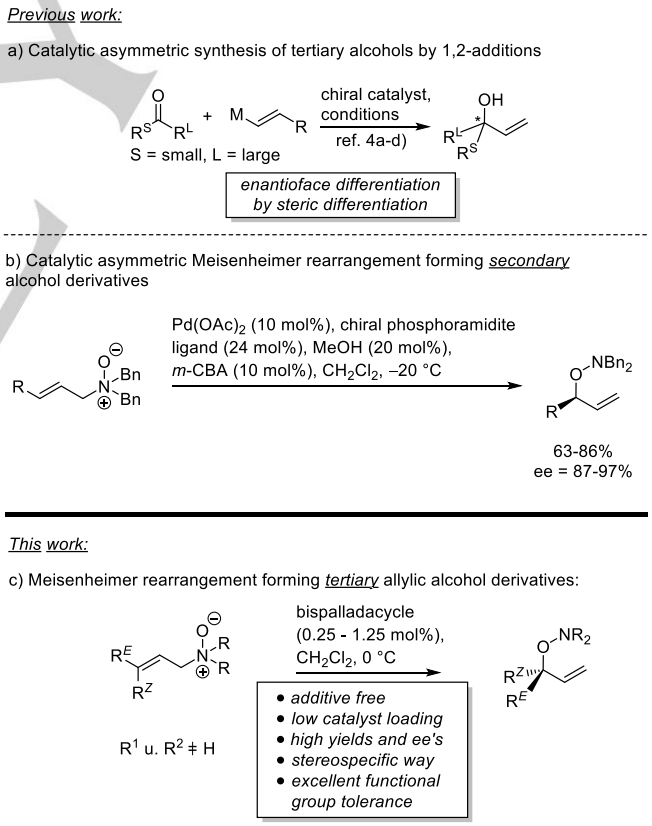
Xin Yu,[a] Nick Wannenmacher,[a] and René Peters*[a]

Abstract: Chiral acyclic tertiary allylic alcohols are very important synthetic building blocks, but their enantioselective synthesis is often challenging. A major limitation in catalytic asymmetric 1,2-addition approaches to ketones is the enantioface differentiation by steric distinction of both ketone residues. In this communication we report the development of a catalytic asymmetric Meisenheimer rearrangement to overcome this problem, as it proceeds in a stereospecific manner. This allows for high enantioselectivity also for the formation of products in which the residues at the generated tetrasubstituted stereocenter display a similar steric demand. Low catalyst loadings were found to be sufficient and the reaction conditions were mild enough to tolerate even highly reactive functional groups such as an enolizable aldehyde, a primary tosylate or an epoxide. Our investigations suggest an intramolecular rearrangement pathway.

Chiral enantiopure allylic alcohols are highly valuable building blocks owing to the enormous synthetic versatility of C=C double bonds.[1] While numerous ways have been described to synthesize secondary allylic alcohols in a highly enantioselective fashion, there are few examples for the challenging catalytic asymmetric synthesis of tertiary allylic alcohols.[1,2] Cyclic tertiary allylic alcohols were, for example, enantioselectively formed from alkynones via tandem addition/cyclization sequences.[2,3] For acyclic products the development of asymmetric additions of reactive vinylmetal reagents to ketones is particularly noteworthy (Scheme 1a)).[2,4] In that case, however, high stereochemical efficiency is limited to substrates, in which either the ketone residues R^S and R^L differ considerably in terms of their steric demand[4a-d] or where the electrophilic keto moiety experiences further activation by a contiguous carbonyl moiety to form a chelate complex.[4e] In addition, high catalyst loadings and large amounts of vinyl(half)metal sources were usually required.

The [2,3]-Meisenheimer rearrangement of allylic *N*-oxides has been described as an alternative approach towards highly enantioenriched allylic alcohols.[5,6] In 2011, the so far only known catalytic asymmetric [2,3]-Meisenheimer rearrangement was published by Tambar et al. (Scheme 1b)).[7] $Pd(OAc)_2$ (10 mol%) and a chiral phosphoramidite ligand (24 mol%) were employed to form secondary allylic alcohol derivatives within a typical reaction time of 2-5 days. Attempts to lower the loadings of $Pd(OAc)_2$ and chiral ligand led to prolonged reaction times and diminished the enantioselectivity. MeOH and *m*-chlorobenzoic acid (*m*-CBA) were necessary to improve the enantioselectivity to *ee* values >90%. Their role in this catalytic process was unknown.[7]

Herein, we report that a planar chiral ferrocene based bispalladacycle, which was developed in our group[8] as catalyst for a number of different applications,[9] efficiently enables the asymmetric formation of tertiary allylic alcohol derivatives by [2,3]-Meisenheimer rearrangements of amine-N-oxides possessing trisubstituted olefin moieties (Scheme 1c)). By this method acyclic tertiary allylic alcohols are accessible with high enantioselectivity, even when the residues R^1 and R^2 display a similar steric demand. Moreover, substrates with very reactive electrophilic functional groups such as aldehyde, epoxide, primary tosylate or ester moieties, etc., which might be problematic in 1,2-addition reactions, were well accommodated.



Scheme 1. Comparison of previous work to this work.

Allylic amine **1a** equipped with a trisubstituted olefin moiety was selected as model substrate (Table 1). *N*-Oxide **2a** was prepared at −20 °C by oxidation with *meta*-chloroperbenzoic acid (*m*-

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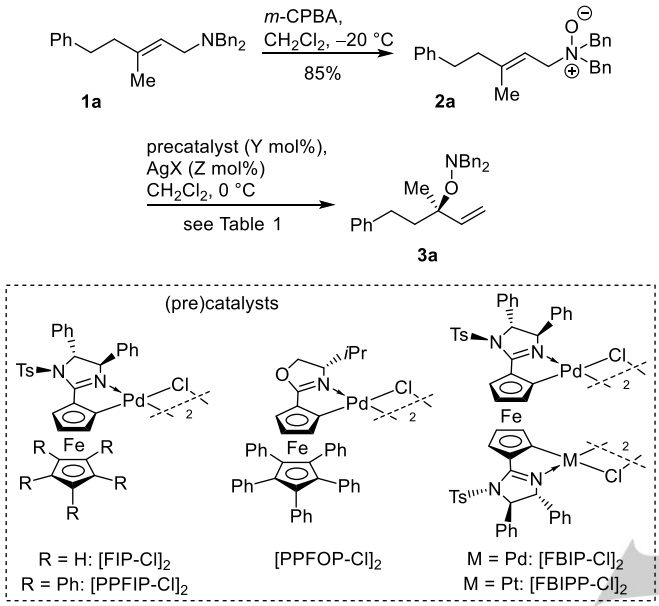
CPBA). Gratifyingly, treatment of freshly prepared **2a** with the planar chiral chloride bridged ferrocenylimidazoline palladacycle $[FIP\text{-}Cl]_2$[10] (2.5 mol%) activated with AgOAc (5 mol%) prior to use by chloride / acetate exchange[11] provided **3a** in high yield (86%) and with promising enantioselectivity (*ee* = 72%, entry 1).

Table 1. Development of the Meisenheimer rearrangement forming a tetrasubstituted stereocenter.



#	(pre)catalyst / AgX	Y; Z	*t* [h][a]	yield[b] **3a** [%]	*ee*[c] **3a** [%]
1	$[FIP\text{-}Cl]_2$ / AgOAc	2.5; 5	80	86	72
2	$[PPFIP\text{-}Cl]_2$ / AgOAc	2.5; 5	80	9	3
3	$[PPFOP\text{-}Cl]_2$ / AgOAc	2.5; 5	80	11	4
4	$[FBIP\text{-}Cl]_2$ / AgOAc	1.25; 5	80	91	93
5	$[FBIPP\text{-}Cl]_2$ / AgOAc	1.25; 5	80	86	93
6	$[FBIP\text{-}Cl]_2$ / AgOMs	1.25; 5	80	89	93
7	$[FBIP\text{-}Cl]_2$ / AgTFA	1.25; 5	80	89	78
8	$[FBIP\text{-}Cl]_2$	1.25; -	90	90	95
9	$[FBIP\text{-}Cl]_2$ / AgOMs	0.5; 2.0	90	92	95
10	$[FBIP\text{-}Cl]_2$	0.5; -	24	92	95
11	$[FBIP\text{-}Cl]_2$	0.25; -	48	82	95

[a] Reaction time of the rearrangement step. [b] Yield of isolated product **3a**. [c] Enantiomeric excess determined by HPLC. $[FIP\text{-}Cl]_2$: chloride bridged ferrocenylimidazoline palladacycle; $[PPFIP\text{-}Cl]_2$: chloride bridged pentaphenylferrocenylimidazoline palladacycle; $[PPFOP\text{-}Cl]_2$: chloride bridged pentaphenylferrocenyloxazoline palladacycle; $[FBIP\text{-}Cl]_2$: chloride bridged ferrocenediylbisimidazoline bispalladacycle; $[FBIPP\text{-}Cl]_2$: chloride bridged ferrocenediylbisimidazoline palladaplatinacycle; OAc: acetate; OMs: mesylate; TFA: trifluoroacetate.

Surprisingly, with the related pentaphenylferrocene containing catalysts generated from $[PPFIP\text{-}Cl]_2$ and $[PPFOP\text{-}Cl]_2$, which are excellent precatalysts for [3,3]-rearrangements of allylic imidates and carbamates,[12-14] only poor activity and enantioselectivity was noted (entries 2 and 3). In contrast, the readily prepared C_2-symmetric bispalladacycle $[FBIP\text{-}Cl]_2$[8,9] (1.25 mol%) activated by AgOAc allowed for high enantioselectivity and yield (entry 4). Similar results were obtained with the mixed dinuclear pallada-/platinacycle $[FBIPP\text{-}Cl]_2$[15] (1.25 mol%) activated by AgOAc (entry 5). Because $[FBIP\text{-}Cl]_2$ is more readily prepared and also more robust, it was selected for further optimization. The use of various anionic ligands by chloride exchange was investigated next. With some of them like mesylate (entry 6), similar results as with acetate were obtained, whereas others led to inferior results (e.g. entry 7). Unexpectedly however, noteworthy catalytic activity was also found with the non-activated $[FBIP\text{-}Cl]_2$ (entry 8). For neutral halide bridged ferrocene palladacycles the activation by halide exchange was often crucial in other application.[16] Some exceptions have been reported for monopalladacycles.[17] In contrast, for the fourfold connected dimeric bismetallacycles, the activation was so far a must to achieve satisfying activity. Next to the practical advantage of avoiding an activation step, non-activated $[FBIP\text{-}Cl]_2$ also allowed for nearly identical enantioselectivity and still displayed useful catalytic activity at reduced catalyst loadings (entries 7-11). Thus, also with 0.25 mol% catalyst an attractive reaction outcome was noticed (entry 11).

For the investigation of the substrate scope, a catalyst loading of 0.5 mol% was chosen for most examples (Table 2). The title reaction was found to be broadly applicable. Next to linear alkyl groups (entries 1 & 2) also α-branched alkyl moieties were tolerated (entries 3 & 4). Moreover, we found a high compatibility with a number of functional groups, including quite sensitive ones. For instance, attractive results in terms of yield and enantioselectivity were still obtained in the presence of an enolizable aldehyde moiety (entry 5), an unprotected alcohol (entry 6), a silyl ether (entries 7 & 13), an electrophilic primary tosylate (entry 8), an enolizable ester (entry 9), a benzylcarbonate (entry 10), a benzyl ether (entries 11, 12, 17), an epoxide (entries 14 & 15) and an olefin moiety (entry 16). As a general trend it was found, that larger residues R^Z slow down the reaction and for that reason a catalyst loading of 1.25 mol% was used in these challenging cases (entries 11-13, 15, 17). The reaction was found to be stereospecific, because geometric olefin substrate isomers resulted in different optical antipodes (entries 14 & 15). For this reason, high enantioselectivity can also be attained employing substrates, in which the residues R^E and R^Z display a similar steric demand (e.g. in entries 11 and 12). This is thus a conceptual advantage compared to the above mentioned 1,2-addition approach.

The reaction type is not limited to dibenzylamine based *N*-oxides as entry 17 shows, in which a diethylamino moiety was employed. However, substrate **2o** is more prone towards thermal rearrangement and the freshly prepared isolated **2o** already contained 1.7% racemic rearrangement product, when the Pd-catalyzed rearrangement was started. This thermal background reaction is also the reason, why the title reaction should be performed at 0 °C.

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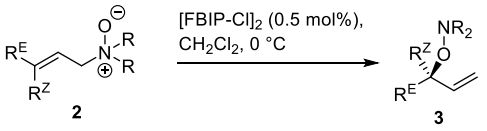
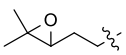
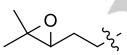
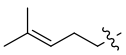
The method is also partly useful in terms of enantioselectivity for substrates with aromatic olefin substituents as shown by entry 18, in which 74% *ee* were attained for R^E = Ph & R^Z = Me. In contrast, for R^E = Me & R^Z = Ph, the *ee* was just 42% (yield 85%, not shown). In order to demonstrate the practical utility, the title reaction was also performed on a bigger scale employing (*Z*)-configured substrate **2m**. In that case, 522.0 mg of product **3m** were isolated (yield 82%) with an *ee* of 88%, which is similar to entry 13.

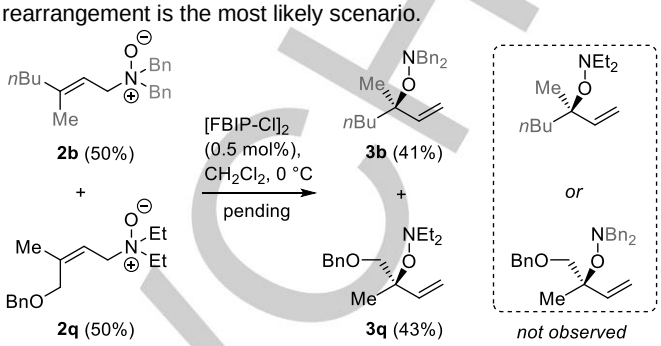
Table 2. Investigation of the substrate scope.



entry	2, 3	R^E	R^Z	R	yield[a] 3 [%]	*ee*[b] 3 [%]
1	**a**	$(CH_2)_2Ph$	Me	Bn	92	95
2	**b**	*n*Bu	Me	Bn	89	91
3[c]	**c**	*i*Pr	Me	Bn	90	90[e]
4[c]	**d**	cyclo-Hex	Me	Bn	83	93[e]
5	**e**	$(CH_2)_2CHO$	Me	Bn	86	91[e]
6	**f**	$(CH_2)_3OH$	Me	Bn	80	89
7	**g**	$(CH_2)_3OTBS$	Me	Bn	85	94[e]
8	**h**	$(CH_2)_3OTs$	Me	Bn	69	93
9	**i**	$(CH_2)_2CO_2Et$	Me	Bn	93	92
10	**j**	$(CH_2)_3OCO_2Bn$	Me	Bn	89	93
11[c]	**k**	*n*Bu	CH_2OBn	Bn	80	92
12[c]	**l**	$(CH_2)_{10}Me$	CH_2OBn	Bn	76	86
13[d]	**m**	Me	$(CH_2)_3OTIPS$	Bn	83	90
14[d]	**n**		Me	Bn	96	83[e]
15[d]	**o**	Me		Bn	96	87[e]
16	**p**		Me	Bn	89	96
17	**q**	Me	CH_2OBn	Et	83	90[f]
18[d]	**r**	Ph	Me	Bn	87	74

[a] Yield of isolated product; typically 20-90 mg scale. [b] Enantiomeric excess determined by HPLC. [c] 1.25 mol% $[FBIP\text{-}Cl]_2$ were used. [d] 1.25 mol% $[FBIP\text{-}OAc]_2$ were used. [e] Determined after derivatization (see Supporting Information). [f] The *N*-oxide **2o** contained 1.7% of racemic rearrangement product at the start. TBS: *tert*-butyldimethylsilyl; OTs: tosylate; TIPS: triisopropylsilyl.

To get insight if the product formation proceeds via an intramolecular rearrangement pathway, cross-over experiments were conducted. A 1:1 mixture of allylic *N*-oxides **2b** and **2o**, which differ in both the *N*-oxide residues and the olefin substituents, was treated with the palladacycle catalyst (Scheme 2). The two expected products for an intramolecular pathway were formed in good and similar yields, whereas cross-over products were not detected by ^{1}H-NMR. Hence an intramolecular rearrangement is the most likely scenario.



Scheme 2. Cross-over experiment pointing to an intramolecular pathway.

Monitoring of the reaction up to conversions of ca. 60% by ^{1}H-NMR spectroscopy revealed a nearly linear relationship between conversion and time (see Supporting Information) indicating a zero order dependence on the *N*-oxide **2a**. A substrate saturation thus appears likely and might be the consequence of a two-point coordination of the substrate in which both the olefin and the *N*-oxide bind to either one or two metal centers. This high coordination affinity might also explain why the usually almost inactive chloride bridged dimer $[FBIP\text{-}Cl]_2$ can be used as a catalyst without prior activation by a silver salt to facilitate the substrate coordination step.[18] Moreover, the linear relationship indicates that product inhibition probably is negligible.

Mass spectrometric investigations (ESI) were performed during the course of the reaction. Palladacycle species possessing accurate masses that would fit to coordination of either one or two substrate molecules were detected after 10 h, but also already 5 min after the start of the reaction, in agreement with a substrate saturation scenario (see SI for details). Nevertheless, ^{1}H-NMR spectra were too complex to identify the precise structure of the resting state.

To showcase that the enantioenriched rearrangement products are valuable precursors toward scalemic tertiary allylic alcohols, the epoxide substituted stereoisomers **3n** and **3o** were transformed into diols **5** and **(*ent*)-5** in good yields by reductive epoxide ring opening and subsequent cleavage of the weak N-O bond by zinc metal (Scheme 3). Moreover, monobenzyl protected diols **4k** and **4l** were prepared in 74 and 94% yield from **3k** and **3l**, respectively, using the latter method. Product **3a** prepared in the model reaction was transformed to **4a** in the same way to determine the absolute configuration by comparison to reported optical rotation data.[19] Comparison of the ee values of **3a** and **4a** also revealed that cleavage of the N-O bond proceeded with only little racemization.

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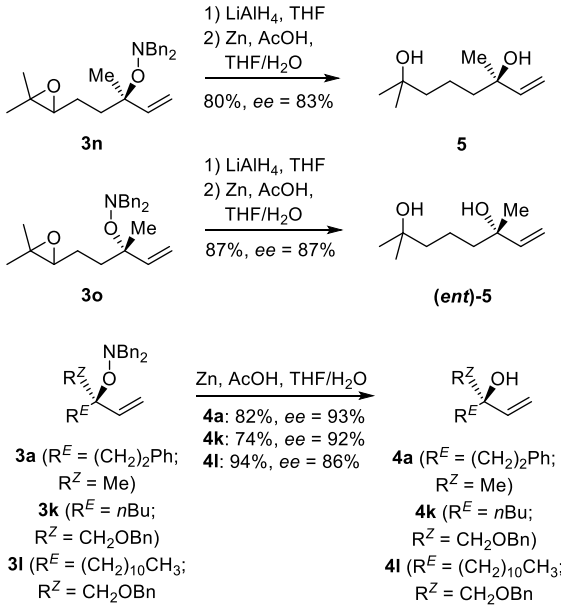

Scheme 3. Synthesis of tertiary allylic alcohols employing the rearrangement products.

In summary, we have reported a catalytic asymmetric Meisenheimer rearrangement as an efficient entry to acyclic tertiary allylic alcohols. This reaction is catalyzed by the robust ferrocene based bispalladacycle catalyst [FBIP-Cl]$_2$ and proceeds in an stereospecific manner. It allows for high enantioselectivity even for the formation of products in which the residues at the generated stereocenter display a similar steric demand. From a practical point of view, this method is also attractive, because no catalyst activation and no catalytic additives are required. Moreover low catalyst loadings were sufficient and the reaction conditions are mild enough to tolerate even highly reactive functional groups. The experimental data suggests an intramolecular rearrangement pathway with a substrate saturation of the palladacycle catalyst.

Acknowledgements

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Keywords: asymmetric catalysis • bimetallic catalyst • palladacycle • rearrangement • tertiary alcohols

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[17] See ref. 12e, 13b.

[18] In combination with the above mentioned stereospecificity, it appears reasonable that the reaction proceeds like already suggested in allyl imidates (see ref. 10 and 14e) and carbamate rearrangements (see ref. 12e) via a face selective coordination of the C=C double bond to a Pd^{II} center and a subsequent stereoselectivity determining C-X bond formation.

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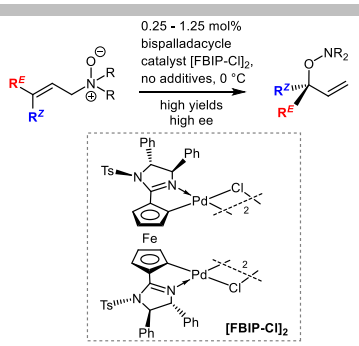
A stereospecific catalytic asymmetric Meisenheimer rearrangement is reported, which allows for high enantioselectivity even for the formation of products in which the residues at the generated tetrasubstituted stereocenter display similar steric demands. Functional groups were well tolerated by the robust, readily available catalyst.



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