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Dynamic Kinetic Resolution of Heterobiaryl Ketones via Zn-catalyzed Asymmetric Hydrosilylation

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Dedicated to Prof. A. Ulises Acuña on the occasion of his retirement

Abstract: A diastereo and highly enantioselective dynamic kinetic resolution (DKR) of configurationally labile heterobiaryl ketones is described. The DKR proceeds by zinc-catalyzed hydrosilylation of the carbonyl group, leading to secondary alcohols bearing axial and central chirality. The strategy relies on the labilization of the stereogenic axis that takes place thanks to a Lewis acid-base interaction between a nitrogen atom in the heterocycle and the ketone carbonyl. The synthetic utility of the methodology is demonstrated through stereospecific transformations into *N,N*-ligands or appealing axially chiral, bifunctional thiourea organocatalysts.

Axially chiral biaryl compounds are important molecular scaffolds present in many natural products and bioactive substances.^[1] Furthermore, they are among the most important class of structures with extensive utility in asymmetric catalysis, particularly as ligands for metals but also as organocatalysts.^[2] The asymmetric coupling of two arene derivatives by cross-coupling or oxidative dimerization is the most straightforward approach for their synthesis,^[3] but these methods lack generality and fail in cases such as the heterobiaryl synthesis. Transition metal-catalyzed dynamic kinetic resolutions (DKR),^[4] the *nov*o construction of aromatic rings,^[5] and a growing number of organocatalytic approaches^[6] have also been reported for specific applications in this field. An appealing DKR strategy consists on the asymmetric ring-opening of biaryl lactones developed by Bringmann (Scheme 1A),^[7] particularly in catalytic variants reported by the groups of Yamada^[8] and Wang.^[9] Closely related DKR strategies are based on racemization via ring-opening/ring-closing events. The Akiyama group realized that biaryl hemiaminals (Scheme 1B) are suitable intermediates for DKR, since they can be easily formed and opened *in situ*.^[10]

Scheme 1. Strategies for the labilization of stereogenic axis in biaryls

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The imine group in the open form can be then reduced by asymmetric transfer hydrogenation reaction. Conversely, this racemization strategy has been recently combined with borrowing hydrogen catalysis for a redox-neutral amination of biaryl compounds.^[11] Clayden and Turner have also reported a biocatalytic DKR of atropoisomeric biaryl N-oxide-aldehydes triggered by a ketoreductase enzyme (Scheme 1C).^[12] This is an appealing strategy to access new heterobiaryl scaffolds, but the dynamic racemization via six-membered transition states can only be performed in systems with reduced steric strain and the method is limited to N-oxides. We have also developed dynamic kinetic Pd-catalyzed C–C, C–P and C–N bond-forming reactions (dynamic kinetic asymmetric transformations, DYKAT) which rely in the labilization of the stereogenic axis as a consequence

of the widening of angles φ_1 and φ_2 in *five membered* cyclic, oxidative addition intermediates (Scheme 1D).^[13] This is also a versatile methodology for the synthesis of axially chiral heterobiaryls, but there is still the need of expensive and toxic Pd-based catalysts. Stimulated by this observation, though, we envisioned that related Lewis acid-base interactions in *five-membered* cyclic intermediates could be exploited for the DKR of heterobiaryl derivatives. In other words, we speculated whether a Lewis acidic functional group could play the role of the metal center in the DYKAT approach. In spite of its modest Lewis acidity, acyl groups are appealing candidates considering the many possible transformations (quaternizations) that would eliminate its Lewis acid character, therefore stabilizing the stereogenic axis. On the basis of this idea, we now wish to report on the dynamic kinetic resolution of heterobiaryl ketones via Zn-catalyzed asymmetric hydrosilylation (Scheme 1E). As a working hypothesis, we anticipated that a relatively fast racemization, associated again with a widening of φ_1 and φ_2 , could take place either via five-membered zwitterionic intermediates **I** or through transition states **II** with a partially developed N–C(carbonyl) covalent bond and an incipient pyramidalization of the carbonyl carbon.

The asymmetric hydrosilylation of ketones is a well established method to obtain secondary alcohols under mild conditions.^[14] Given the number of catalytic systems available, many of them based in nonprecious metals,^[15] this reaction was chosen as the first option to explore our hypothesis. The model substrate **2a** was easily synthesized by Pd-catalyzed Heck reaction of the known triflate *rac*-**1a** with butyl vinyl ether and subsequent hydrolysis of the resulting coupling product (Scheme 2). X-Ray diffraction analysis of **2a**^[16] showed the presence of both atropoisomers in the solid state, but the analysis by chiral HPLC pointed to their configurational lability in solution: a single

Table 1. Screening of Reaction Conditions and Ligands.^[a]

2a: *racemic, configurationally labile*

2a: *racemic, configurationally labile*

Ligands:

L1: R = CH₃
L2: R = Bn
L3: R =
L4: R =
L5: R =
L6: R =

Entry ^[a]	L	T (°C)	time (h)	conv. (%) ^[b]	dr ^[b]	ee (%) ^[c] major/minor
1	L1	20	24	>99	2:1	40/54
2	L1	0	24	85	2:1	59/44
3	L2	20	48	6	n.d.	n.d./n.d.
4	L2	65	36	>99	5:1	83/52
5	L3	66	36	>99	4:1	72/31
6	L4	66	36	>99	5:1	85/53
7	L5	66	36	>99	4:1	91/72
8	L6	66	36	>99	5:1	98/89
9 ^[d]	L6	66	36	>99	5:1	98/90
10 ^[e]	L6	66	36	<5	n.d.	n.d.
11 ^[f]	L6	66	36	<5	n.d.	n.d.

[a] Reactions at 0.1 mmol scale. [b] Determined by ¹H NMR spectroscopy. [c] Determined by HPLC. [d] Zn(OAc)₂ (5 mol%)/L6 (6 mol %). [e] PMHS was used instead of (EtO)₂MeSiH. [f] PhMe₂SiH was used instead of (EtO)₂MeSiH

narrow peak was regularly observed using a large variety of chiral stationary phases and elution conditions. Reduction of **2a** with NaBH₄ afforded a 1:1 mixture of diastereomeric alcohols **3a**; HPLC analysis of this mixture revealed four distinct peaks corresponding to all possible stereoisomers. This behavior, in contrast to that observed for **2a**, confirms the configurational stability of **3a**. An additional proof for the configurational lability of **2a** was obtained after hydrolysis of the enantioenriched (92% ee) vinyl ether **4**.^[17] Interestingly, this reaction requires a slow addition of the substrate over an excess of aq. HCl (conditions a). Otherwise (conditions b), unexpected isoquinolinium salt **5** is obtained as the major product. This product closely resembles the zwitterionic intermediate **I** that, likewise, has lost the chiral information of the stereogenic axis. Additionally, reduction of the ketone **2a** obtained from **4** afforded again the mixture of racemic diastereomers **3a**. Control experiments showed that alcohols **3** do not epimerize/racemize under these reductive conditions. Consequently, it can be deduced that ketone **2a** quickly racemizes after hydrolysis of the parent vinyl ether **4**. Further experiments and a DFT analysis for the atropoisomerization of **2c** were also conducted, and the results (see the supporting information for details) are fully consistent with the starting hypothesis: according to this study, the racemization takes place via a 'quasi zwitterionic' transition state (type **II**) with a relatively low barrier of 22.1 kcal mol⁻¹.^[18]

With this key information in hand we started the screening of conditions for the asymmetric hydrosilylation of the model substrate **2a** (Table 1). A first interesting result was observed by using inexpensive and environmentally benign $\text{Zn}(\text{OAc})_2$ ^[19] in combination with (*S,S*)-*N,N'*-dimethyl 1,2-diphenylethylene-diamine ligand **L1**: a 2:1 diastereomeric mixture of products **3a** with a 40% ee for the major isomer was observed using 2 equivalents of $(\text{EtO})_2\text{MeSiH}$ in THF at 20 °C (entry 1). At lower temperature (0 °C, entry 2) the conversion dropped and no significant improvement was observed (entry 2). The easy synthesis and structural modularity of this type of *N,N* ligands, however, facilitated further optimization.^[20] A surprising lack of reactivity at rt was observed by introducing benzyl groups in the chiral scaffold (**L2**, entry 3). Nevertheless, full conversion with 5:1 diastereoselectivity and a promising 83% ee for the major isomer were achieved by simply heating the reaction to reflux (entry 4). Ligand **L3** with additional *tert*-butyl groups at the *para* positions of the benzyl units afforded a slightly lower selectivity (entry 5) while ligand **L4** bearing four *meta* methoxy groups afforded a similar result (entry 6). A significant improvement was observed for ligands **L5** with *ortho* methyl groups (91% ee, entry 7). Finally, use of ligand **L6**, bearing four bulky *tert*-butyl groups in the *meta* positions, yielded **3a** with excellent conversion and high diastereo- and enantioselectivity (entry 8). Moreover, the catalyst loading could be reduced to 5 mol% to obtain a similar result (Entry 9). Noteworthy, alternative silanes such as polymethylhydrosiloxane (PMHS) and PhMe_2SiH were unreactive in this transformation (entries 10,11).

Under optimized conditions, the scope of the process was explored for different heterobiaryl scaffolds and acyl groups (Table 2). Ketone **2b** bearing a methyl group at position 4 of the naphthalene ring performed very similar to the model ketone **2a**, affording alcohol **3b** in 80% yield, 4.5:1 dr, and a 97% ee for the major diastereomer (entries 1 and 2). Alcohols **3c** and **3d**, derived from 1-(1-naphthyl)picoline and 1-(*o*-tolyl)isoquinoline derivatives, respectively, could also be obtained in high yields and enantioselectivities (entries 3 and 4). Remarkably, 1-(1-naphthyl)quinazoline derivative **2e** afforded the corresponding alcohol with a higher 8.5:1 diastereoselectivity. Due to its high polarity, the crude alcohol **3e** was acetylated ($\text{Ac}_2\text{O}/\text{DMAP}$) before purification, yielding a mixture of the expected *O*-acetyl derivative **3'e** and product **3''e**, formally resulting from *N*-acylation and intramolecular 1,2 addition of the hydroxyl group. Heterobiaryl methyl ketone **2f** bearing a phenyl group in position 3 was also well tolerated, although a slightly lower diastereoselectivity was observed (entry 6). More sterically demanding methyl 1-(1-pyrenyl)-isoquinoline ketone **2g** also underwent hydrosilylation of the carbonyl affording **3g** in high yield and enantioselectivity, (entry 7). Moreover, ketones **2h-j** bearing different aliphatic substituents also provided the desired products in high yields and enantiomeric ratios (entries 8-10). Interestingly, a 20:1 dr was observed for the more sterically demanding neopentyl ketone **2i** although with decreased enantioselectivity (80% ee). It is worth to stress that in all cases, without exception, the two diastereomers were readily isolated in pure form after a simple column chromatography. *Importantly, the hydrosilylation of 2a was also performed on a bigger scale (1 mmol) affording 3a in better yield (95%, 77% of isolated major isomer), and diastereoselectivity (5.3:1) without compromising*

Table 2. Substrate scope.^[a]

entry ^[a]	SM	dr ^[b]	yield ^[c]	prod	ee _{major} (%) ^[d]	ee _{minor} (%) ^[d]
1	2a	5:1	77(67)	3a	97	90
2	2b	4.5:1	80(64)	3b	97	89
3	2c	4:1	93(78)	3c	96	82
4	2d	3.2:1	80(61)	3d	90	88
5	2e	8.5:1	66	3'e/3''e ^[e]	98/97	-
6	2f	2:1	91(59)	3f	95	95
7	2g	3.2:1	88(70)	3g	97	86
8	2h	4:1	86(70)	3h	94	94
9	2i	>20:1	52	3i	80	-
10	2j	2.5:1	86(63)	3j	91	88
11	2a	5.3:1	95(77)	3a	97	90

[a] All reactions reached full conversion as determined by TLC and ¹H NMR spectroscopy. [b] Determined by ¹H NMR in the crude reaction mixtures. [c] Isolated overall yields after chromatography. In parenthesis, yield of pure major isomer [d] Determined by HPLC. [e] **3'e** and **3''e** were isolated in 41% and 25% yield, respectively.

the excellent enantioselectivities (entry 11). The absolute configuration of (*R,R*)-**3a** and (*R,R*)-**3''e** were determined by X-ray diffraction analysis,^[16] while that of the minor isomer (*S,S*)-**3a** was assigned by chemical correlation.^[21] The absolute configurations of other products **3** were assigned by analogy. The newly synthesized heterobiaryl alcohols with both central and axial chirality offer many possibilities for further functionalization and are highly useful synthons for the synthesis of various chiral heterobiaryls that are otherwise difficult to access. Representative transformations from (*R,R*)-**3a** are

shown in Scheme 3. Displacement of the secondary alcohol using diphenylphosphoryl azide (DPPA) and DBU was carried out to obtain azide ((R_a,S) -7^[16] with inversion of the configuration at the stereocenter. A unique class of chiral N,N -ligand ((R_a,S) -8 was prepared via Cu(I)-catalyzed cycloaddition reaction of (R_a,S)-7 with phenylacetylene in good yield under mild conditions. Moreover, Staudinger reduction of (R_a,S)-7 furnished amine ((R_a,S) -9, an appealing homologue of the ligand IAN,^[13d,22] but incorporating an additional stereocenter. Finally, a novel class of bifunctional thiourea catalysts ((R_a,S) -10 was easily

Scheme 3. Representative transformations from (R_a,R)-3a.

obtained by condensation of (R_a,S)-9 and 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene. Importantly, the enantiomeric purity in these products was completely preserved during these reaction sequences.

In conclusion, a weak Lewis acid-base interaction is the key for the atroposelective Zn-catalyzed hydrosilylation of heterobiaryl ketones via dynamic kinetic resolution. The resulting heterobiaryl carbinols containing both central and axial stereogenic elements are also direct precursors for the synthesis of chiral bidentate ligands and bifunctional thiourea-based organocatalysts. The development of related catalytic reactions based on this racemization strategy is currently under investigation in our laboratories.

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Keywords: asymmetric catalysis • dynamic kinetic resolution • axial chirality • hydrosilylation • ligand design

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- [16] CCDC 1589898 (**2a**), 1589899 [(*R_s*,*R*)-**3a**], 1589900 [(*R_s*,*S*)-**7**] and 1813056 [(*R,R*)-**3''e**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif
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Entry for the Table of Contents

COMMUNICATION

The dynamic duo: A nitrogen atom and the carbonyl group in heterobiaryl ketones form a Lewis pair responsible for the labilization of the stereogenic axis, which constitutes the key strategy to develop a Zn-catalyzed asymmetric hydrosilylation *via* dynamic kinetic resolution. This process simultaneously installs a stereogenic axis and a stereocenter for the highly enantioselective synthesis of heterobiaryl carbinols.

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Page No. – Page No.

Dynamic Kinetic Resolution of Heterobiaryl Ketones via Zn-catalyzed Asymmetric Hydrosilylation