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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
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Catalytic Asymmetric Dearomatizing Redox Cross Coupling of Ketones with Aryl Hydrazines Giving 1,4-Diketones

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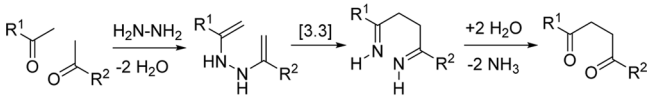
Supporting Information

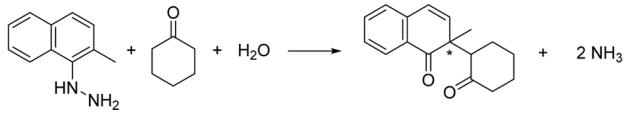
ABSTRACT: An asymmetric Brønsted acid catalyzed dearomatizing redox cross coupling reaction has been realized, in which aryl hydrazines react with ketones to deliver 1,4-diketones, bearing an all-carbon quarternary stereocenter in high enantiopurity.

The Fischer indolization[1,2] can be described as an internal redox reaction in which a carbon−carbon σ-bond is oxidatively generated at the expense of a reductively cleaved nitrogen−nitrogen bond. In this sense, it resembles the dehydrogenative α-cross coupling of two ketones giving highly valuable 1,4-diketones.[3] These considerations and our recent studies on asymmetric catalytic variants of the Fischer indolization[4] guided us toward the conceptual design of a new 1,4-diketone synthesis from two ketones and hydrazine. We report here a first fruition of this concept, with a catalytic asymmetric dearomatizing redox cross coupling reaction of aryl hydrazines and ketones, furnishing enantioenriched 1,4-diketones.

Concept: oxidative redox cross coupling via [3.3]-diaza Cope rearrangement



Here: dearomatizing redox cross coupling of aryl hydrazines with ketones



Dearomatization reactions have received considerable attention in the past few years. Such processes are attractive as they are based on easily accessible starting materials, which are readily transformed into complex, functionalized products.[5,6] While nonasymmetric dearomatization reactions are well explored, catalytic asymmetric approaches are still challenging and have previously been mainly achieved via transition metal catalysis.[6] Organocatalytic fluorinative and oxidative dearomatization reactions have also been described.[7]

The Fischer indolization is inherently a dearomatizing process, generating nonaromatic intermediates after the initial [3,3]-sigmatropic diaza-Cope rearrangement.[2,4] These intermediates normally undergo a rearomatization to the indole by tautomerization and ammonia release. Ortho-substituents at the arylhydrazine would be expected to prevent this rearomatization by generating an α-quaternary center during the rearrangement. However, it has previously been shown that under the normal, forcing acidic conditions, alkyl shifts occur that again lead to an indole.[2,8] We hypothesized that, with the exceptionally mild conditions previously established for our asymmetric indolizations,[4] the generated diimine intermediate should be sufficiently stable such that instead of the alkyl-shift, a hydrolysis would occur, furnishing desirable 1,4-diketones.

Indeed, when we reacted naphthyl hydrazine **1a** and cyclohexanone **2a** in the presence of the weakly acidic resin Amberlite CG50[4a,c,d] and different BINOL-derived phosphoric acids (**4a**−**c**),[9,10] the desired product **3a** was formed enantioselectively (Table 1, entry 1−3). Changing to the SPINOL-derived phosphoric acid (*R*)-**STRIP** (**5c**),[11] compound **3a** could be obtained with an increased enantioselectivity of 95.2:4.8 and a yield of 40% (Table 1, entry 6). We therefore decided to use (*R*)-**STRIP** as catalyst for further optimizations. Using 5 mol % of (*R*)-**STRIP**, different solvents and additives were investigated. Interestingly, the addition of 1 equiv of benzoic acid led to an improved yield of 52%, without lowering the enantioselectivity (Table 1, entry 7).[12] As expected from the stoichiometry of the reaction, the addition of water turned out to be necessary, and 10 equiv of H_2O were found to be optimal in terms of yield and enantioselectivity (Table 1, entry 9), while higher or lower amounts led to a decrease in enantioselectivity or yield, respectively. Lowering the reaction temperature to 40 °C and decreasing the benzoic acid amount to 0.3 equiv slightly improved the yield without influencing the enantioselectivity (Table 1, entry 11). The addition of 1000 mg/mmol of resin proved ideal, with either lower or higher loadings leading to decreased yields (see the Supporting Information). Performing the reaction in *p*-xylene, product **3a** was obtained in 72% yield and with an enantiomeric ratio of 96:4 (Table 1, entry 14).

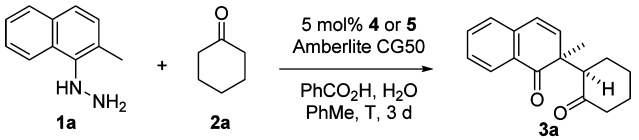
With the optimized conditions in hand, we investigated the scope of this transformation for different hydrazines and ketones (Scheme 1). Cyclohexanones **2a**−**c** reacted smoothly with hydrazine **1a** generating the corresponding diketones **3a**−**c** in good yields and with high stereoselectivities. A cyclic ketal group (**3c**) is well tolerated.

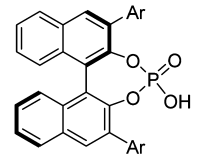
Also, heterocyclic ketones are suitable substrates for this transformation. Thio-substituted ketone **2d** delivers the corresponding diketone **3d** with a high enantiomeric ratio of 97:3, while the corresponding oxygen-substituted product **3e** showed a decreased enantioselectivity of 87.3:12.7. Also the use of nitrogen-containing ketones is possible, generating the

Received: November 5, 2014
Published: February 25, 2015

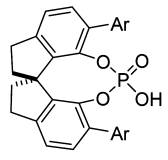
DOI: 10.1021/ja511200j
J. Am. Chem. Soc. 2015, 137, 3446−3449

Table 1. Optimization of the Reaction Conditions[a]





4a: Ar = 2,4,6-(iPr)$_3$-C$_6$H$_2$
4b: Ar = 9-phenanthryl
4c: Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$



5a: Ar = 1-pyrenyl
5b: Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$
5c: Ar = 2,4,6-(iPr)$_3$-C$_6$H$_2$

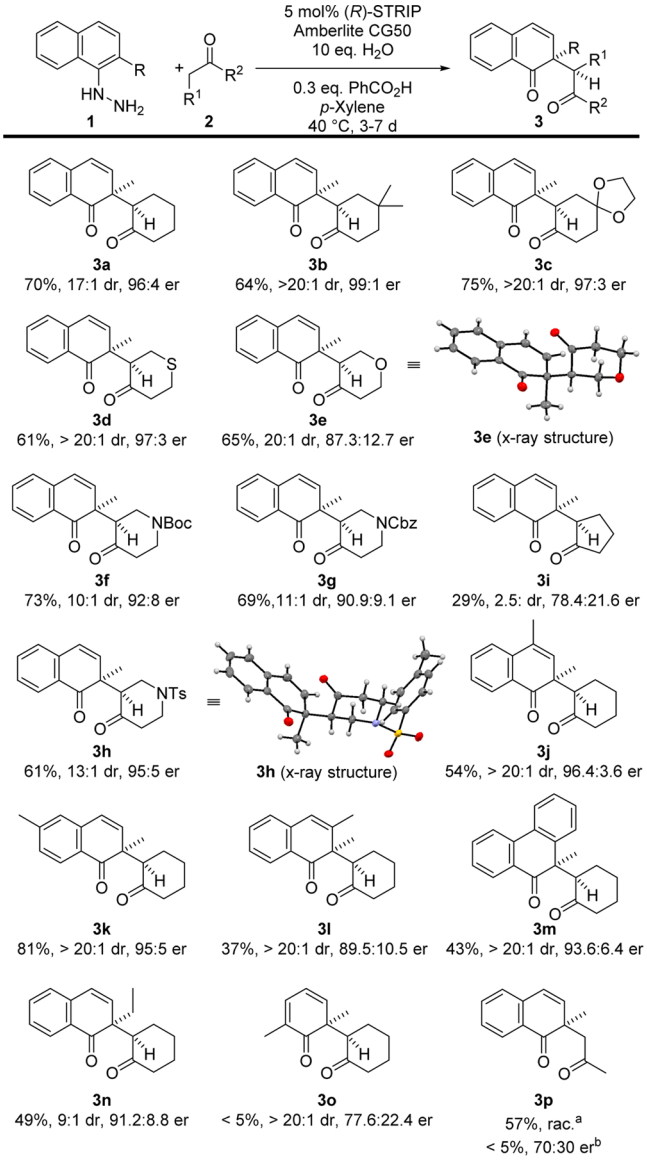
entry	cat.	H_2O	$PhCO_2H$	T(°C)	yield[b]	er[c]
1	**4a**			45	43%	82:18
2	**4b**			45	20%	76.3:23.7
3	**4c**			45	48%	77:23
4	**5a**			45	40%	82:18
5	**5b**			45	44%	58.5:41.5
6	**5c**			45	40%	95.2:4.8
7	**5c**		1 equiv	45	52%	95.1:4.9
8	**5c**	1 equiv	1 equiv	45	55%	94.6:5.4
9	**5c**	10 equiv	1 equiv	45	65%	94.4:5.6
10	**5c**	20 equiv	1 equiv	45	62%	91.3:8.7
11	**5c**	10 equiv	0.3 equiv	40	66%	95:5
12	**5c**	10 equiv	0.3 equiv	30	67%	93:7
13[d]	**5c**	10 equiv	0.3 equiv	40	56%	95:5
14[e]	**5c**	10 equiv	0.3 equiv	40	72%	96:4

[a]Reactions were conducted on a 0.05 mmol scale with 50 mg of Amberlite CG50. The diastereomeric ratio was determined from NMR spectroscopy of the crude reaction mixture (dr > 10:1 in all cases). [b]NMR yield using $CHCl_2CHCl_2$ as internal standard. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Benzene was used as the solvent. [e]p-Xylene was used as the solvent.

corresponding diketones **3f–h** in good yields and enantioselectivities. The structure and absolute configuration of products **3e** and **3h** could be assigned by X-ray crystallography (see the Supporting Information).[13] The change from cyclohexanones to cyclopentanone **2i** leads to a diminished reactivity and stereocontrol (**3i**), while the use of alternative hydrazines delivers the desired products **3j–n** in good yields and enantioselectivities. We also investigated the reaction of one phenyl hydrazine. Unfortunately, though not entirely unexpected, moderate enantioselectivity and poor yield was observed when (2,6-dimethylphenyl)hydrazine **1o** reacted with cyclohexanone. Also the use of acyclic ketones remains challenging, although product **3p** could be obtained in good yield, using simple acetone as ketone in the presence of diphenyl phosphate. Initial results show that it is also possible to access the desired product applying a chiral phosphoric acid as catalyst. Using 20 mol % of catalyst **5b**, diketone **3p** could be obtained in low yield but with a promising enantiomeric ratio of 70:30.

As suggested above, we assume our reaction to proceed via a Fischer-type [3,3]-sigmatropic diaza-Cope rearrangement of the protonated ene hydrazine intermediate **A** to give diimine **B**. At this point, rearomatization to the corresponding indole is interrupted,[14−16] leading to the corresponding hydrolysis product **3**. The generally observed high diastereoselectivity of this new transformation can be explained by considering the

Scheme 1. Scope of the 1,4-Diketone Synthesis



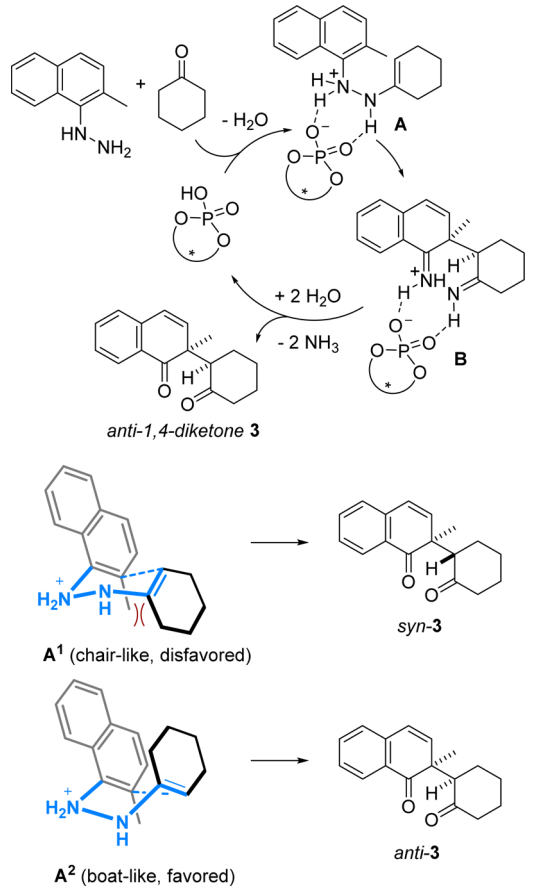
[a]Reaction was conducted with 2 equiv of diphenyl phosphate. [b]Reaction was performed using 20 mol % of catalyst **5b** at 50 °C for 3 d in toluene.

different possible conformations of the enehydrazine that engages in the [3,3]-sigmatropic rearrangement. The diaza-Cope rearrangement can reasonably proceed either via a chairlike (**A**^{1}) or a boatlike (**A**^{2}) conformation of the protonated enehydrazine intermediate (Scheme 2). Apparently, the axial substituent in **A**^{1} causes steric repulsion with the cyclohexene ring, leading to a less favored conformation. In contrast, the [3,3]-sigmatropic rearrangement from the boatlike conformation **A**^{2} should proceed smoothly generating the observed *anti*-1,4-diketone. The dearomatization process is under kinetic control, and no epimerization of the 1,4-diketone product was found under the reaction conditions (see the Supporting Information for details).

In conclusion, we have developed a mild and efficient catalytic asymmetric dearomatization reaction, generating enantioenriched 1,4-diketones, bearing an all-carbon quaternary stereocenter. This approach offers a completely new access

DOI: 10.1021/ja511200j
J. Am. Chem. Soc. 2015, 137, 3446−3449

Scheme 2. Proposed Mechanism and Stereochemical Model



to 1,4-diketones, which are important scaffolds in synthetic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization, NMR spectra, HPLC traces, and X-ray data for **3e** and **3h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous support by the Max-Planck-Society and the European Research Council (Advanced Grant "High Performance Lewis Acid Organocatalysis, HIPOCAT") is gratefully acknowledged. We also thank the members of our NMR, MS, and crystallography departments for their support.

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DOI: 10.1021/ja511200j
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DOI: 10.1021/ja511200j
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