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Dynamic Kinetic Asymmetric Amination of Alcohols: From A Mixture of Four Isomers to Diastereo- and Enantiopure α-Branched Amines

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Supporting Information

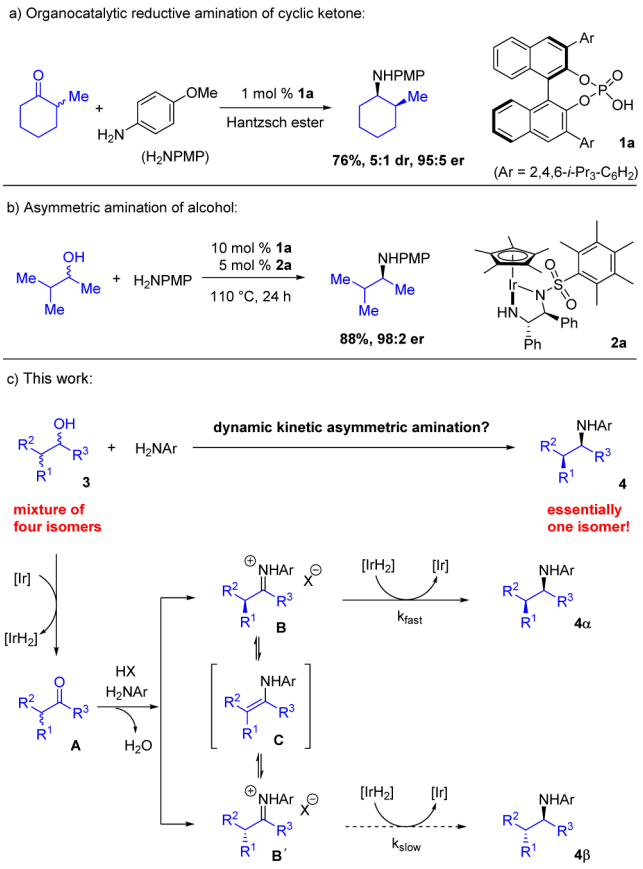
ABSTRACT: The first dynamic kinetic asymmetric amination of alcohols via borrowing hydrogen methodology is presented. Under the cooperative catalysis by an iridium complex and a chiral phosphoric acid, α-branched alcohols that exist as a mixture of four isomers undergo racemization by two orthogonal mechanisms and are converted to diastereo- and enantiopure amines bearing adjacent stereocenters. The preparation of diastereo- and enantiopure 1,2-amino alcohols is also realized using this catalytic system.

Dynamic kinetic asymmetric transformation (DYKAT)[1] or dynamic kinetic resolution (DKR)[2] has proven to be a highly valuable strategy in asymmetric synthesis, as it converts both enantiomers of a racemic substrate into enantioenriched product and overcomes the limitation of 50% theoretical yield in traditional kinetic resolution.[3] Such stereoconvergent processes require a rapid racemization of the substrate (or an intermediate) or the conversion of the racemic substrate to an achiral intermediate prior to the enantio-determining step.[4] Out of various strategies developed for such transformations, racemization of tertiary stereocenters α to carbonyl or imine functionality through the achiral enolate[5] or enamine[6] (as reported from the groups of Noyori, Zhou, Johnson, List and others) and metal-catalyzed racemization of alcohols through a redox process (as reported by the Bäckvall group, the Fu group and others)[7] have found wide application in asymmetric catalysis.[8] One representative example of reductive amination of α-branched cyclic ketones catalyzed by chiral phosphoric acid **1a** is shown in Scheme 1a.[6e] In a few rare cases, a "double" DKR process could be realized in which two isolated stereocenters in the substrate are racemized using the same strategy to yield chiral alcohols bearing multiple stereocenters.[5g,7c,e] We report here a unique system in which α-branched alcohols (easily prepared as a mixture of four stereoisomers) undergo racemization by two orthogonal mechanisms to produce diastereo- and enantiopure acyclic amines and amino alcohols bearing two adjacent stereocenters.

Recently our group reported the first example of catalytic asymmetric amination of alcohols via borrowing hydrogen promoted by Ir-complex **2a** in combination with TRIP **1a** (Scheme 1b).[9a] The groups of Dong and Guan also reported highly efficient Ru-catalyzed diastereoselective amination of alcohols using Ellman's chiral *t*-butanesulfinamide.[9b] Such a process using borrowing hydrogen methodology[10,11] has long been recognized as a highly atom economical and green method for the production of amines, as the alcohol substrate is utilized as the hydrogen donor and no external reductant is required for this transformation.[12] In our enantioselective variant, both enantiomers of the racemic alcohol were converted to enantioenriched amine product through a redox DYKAT pathway (dehydrogenation of the alcohol to ketone, condensation of ketone to form imine followed by asymmetric transfer hydrogenation of imine).

In an effort to extend the synthetic utility of this catalytic system, we became interested in the asymmetric amination of alcohol **3** that can be easily prepared as a mixture of four stereoisomers (Scheme 1c). It was envisioned that the two

Scheme 1. Rationale for Dynamic Kinetic Asymmetric Amination of Alcohols



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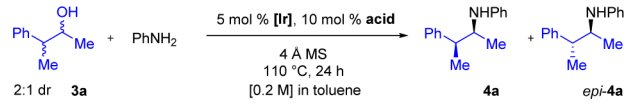
stereocenters in **3** could both be racemized via first oxidation to ketone **A** and then tautomerization of the iminium intermediate (**B** and **B′**) through enamine **C**. Such a process, however, challenges the catalyst with an additional dimension of selectivity in the asymmetric reduction step: it has to differentiate between **B** and **B′**, in addition to the enantiotopic faces of the imine moiety in order to realize high diastereo- and enantioselectivity for the synthesis of **4**.

Intrigued by this possibility of a highly stereoconvergent transformation, we initiated our studies by examining the reaction of **3a** (as a 2:1 mixture of diastereomers) with aniline to generate chiral amine **4a** (Table 1). Preliminary studies

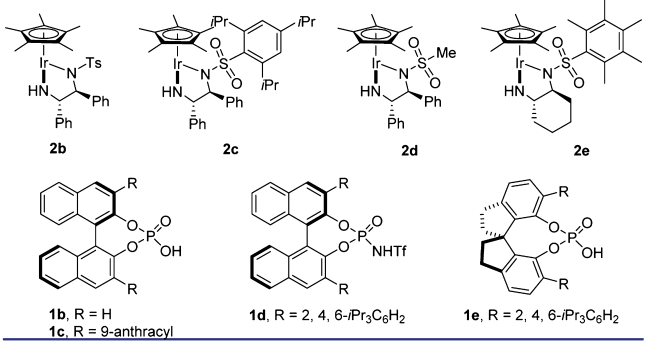
Table 1. Optimization of DYKAT



2:1 dr **3a** **4a** *epi*-**4a**

entry	[Ir]	acid	**3a**:aniline	yield (%)[a]	dr[b]	er[c]
1[d]	**2a**	**1a**	1.5:1	29	89:11	97:3
2	**2a**	**1a**	1.5:1	74	86:14	96:4
3	**2a**	**1a**	1.2:1	72	86:14	96.5:3.5
4	**2a**	**1a**	1.1:1	32	86:14	97:3
5	**2b**	**1a**	1.2:1	19	80:20	91.5:8.5
6	**2c**	**1a**	1.2:1	62	80:20	91:9
7	**2d**	**1a**	1.2:1	8	75:25	62:38
8	**2e**	**1a**	1.2:1	16	67:33	49:51
9	**2a**	**1b**	1.2:1	24	33:67	70:30
10	**2a**	**1c**	1.2:1	6	50:50	74:26
11	**2a**	**1d**	1.2:1	22	50:50	91:9
12	**2a**	**1e**	1.2:1	73	97:3	98.5:1.5
13	**2a**	**1e**	1:1.2	48	97:3	99:1
14	*ent*-**2a**	**1e**	1:1.2	31	86:14	10:90
15[e]	**2a**	**1e**	1:1.2	60	97:3	99:1
16[e,f]	**2a**	**1e**	1:1.2	81	97:3	99:1

[a]Isolated yield. [b]The dr value was determined by NMR spectroscopy of the crude reaction mixture. [c]The er value was determined by HPLC on a chiral stationary phase. [d]*t*-Amyl alcohol as the solvent. [e][0.4 M] concentration. [f]60 h reaction time.

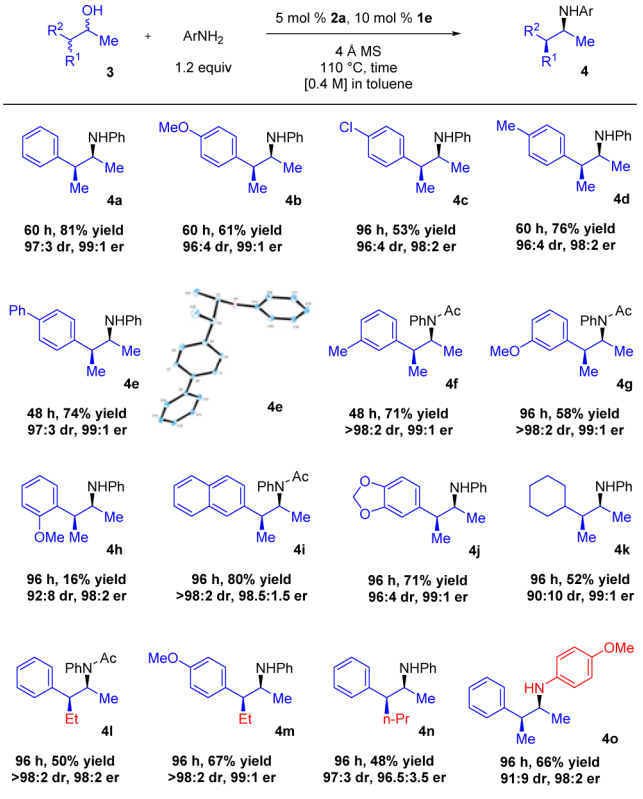


showed that the optimal conditions from our previous studies (*t*-amyl alcohol as solvent)[9a] produced **4a** in a good dr of 89:11 and excellent enantioselectivity, albeit with a low yield (entry 1). As the mixture of **4a** and *epi*-**4a** cannot be easily separated, we set our goal for achieving both high stereoselectivity and high efficiency of the system. After screening various solvents, toluene proved to be the preferred choice that produced **4a** in much enhanced efficiency with slightly decreased stereoselectivity (entry 2). The use of slight excess of **3a** (1.2 equiv or higher) vs aniline was necessary at this stage to maintain the high efficiency (entry 3 vs entry 4), while the dr remained moderate (86:14).

Further efforts to optimize the diastereoselectivity focused on the screening of catalyst structures. Iridium complexes **2b** to **2e** bearing different sulfonamide moiety or chiral diamine backbone all proved to be much less efficient and less stereoselective (entries 5−8).[13] As for the chiral phosphoric acid, the bulky tri-isopropylphenyl substituent in **1a** proved uniquely effective, as **1b** or **1c** turned out to be much less reactive and selective (entries 9−10). Catalyst **1d** that was reported to be more acidic than the corresponding **1a** again showed reduced reactivity and selectivity (entry 11).[14] Finally different chiral backbones of the phosphoric acid were tested. To our excitement, the use of spirocyclic **1e**[15] produced **4a** in excellent dr of 97:3 and er of 98.5:1.5 (entry 12). At this point, the use of **3a** as the limiting reagent proved successful, however, the yield of **4a** reduced to 48% (entry 13). Consistent with our previous studies,[9a] the use of *ent*-**2a** and **1e** proved to be the mis-matched case that resulted in lower stereoselectivity (entry 14). Gratifyingly, more concentrated conditions and a prolonged reaction time led to marked improvement (entries 15−16). The yield of **4a** was improved to 81% with excellent stereoselectivity, realizing a formal conversion of four isomers of **3a** to essentially one stereoisomer of **4a**.

With the optimal conditions in hand, we moved on to examine the scope of this dynamic kinetic asymmetric amination system (Scheme 2). Various *para*-substitutents on

Scheme 2. Scope of Dynamic Kinetic Asymmetric Amination of Alcohols[a]



[a]See SI for the detailed procedure. Some products were converted to the corresponding amide (2.0 equiv DIPEA, 2.0 equiv AcCl, DCM, 3 h) to determine the er. The reported yields refer to the two-step combined yield.

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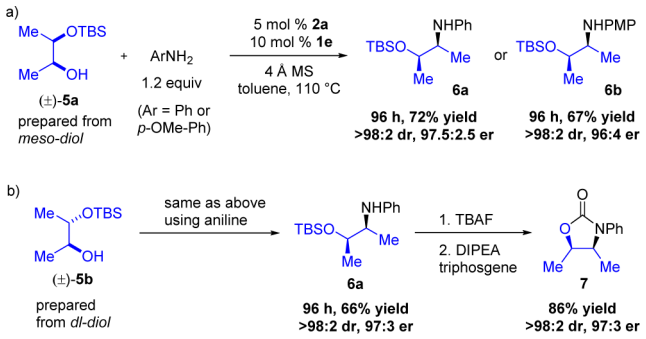
the aryl ring that are electron-donating, electron-withdrawing and electron-neutral can be well-tolerated to yield **4b**−**4e** in uniformly good yield and excellent stereoselectivity. The relative and absolute configuration of **4e** was unambiguously assigned by single crystal X-ray analysis, and those of other products were assigned by analogy. Chiral amines with a *meta*-substituent on the aryl ring (**4f**, **4g**) and also other aryl groups (**4i** and **4j**) were produced with similar success. *Ortho*-substitution on the aryl ring, however, proved to be too sterically hindered; low yield as well as reduced diastereoselectivity was obtained for **4h**.[16] Extension to alkyl, alkyl-substitution at the α-position such as **4k** also worked out well, albeit with a reduced dr of 90:10. Gratifyingly, the smaller substituent on the α-stereocenter can be extended to alkyl groups bigger than methyl (as in **4l**−**4n**) with excellent results. Finally, *p*-anisidine can also be used instead of aniline to produce **4o** with slightly reduced stereoselectivity to that of **4a**.

To further extend the synthetic utility of this system, we examined the reaction using monoprotected diols in an effort to access diastereo- and enantiopure 1,2-amino alcohols. As shown in Scheme 3a, we chose the readily available mono TBS-ether

Scheme 3. Access to Chiral Amino Alcohols



of *meso*-2,3-butanediol **5a** as the model substrate with the hypothesis that the catalyst can recognize the steric difference between the bulkyl siloxy group and methyl to realize high diastereoselectivity. As it turned out, the standard reaction conditions delivered protected amino alcohols **6a** and **6b** (by using aniline or *p*-anisidine, respectively) in good yield and again excellent stereoselectivity. To confirm the reaction outcome is independent of the stereochemistry from the substrate, **5b** derived from the *dl*-diol was also subjected to the standard conditions. This led to the formation of the same product **6a** in similar yield and selectivity (Scheme 3b). **6a** could be converted to the cyclic carbamate **7** by a simple two-step procedure in high efficiency without any loss of stereochemistry.

In summary, we have developed a highly efficient dynamic kinetic asymmetric amination of α-branched alcohols using borrowing hydrogen methodology. Under the cooperative catalysis of an iridium complex with a chiral phosphoric acid, the mixture of four isomers in the alcohol substrate is converted to diastereo- and enantioenriched acyclic chiral amines in a highly convergent fashion. Current efforts in our laboratories are focused on further extension of this method to access more functionalized molecules and the development of new and more effective catalysts (especially those based on first-row transition metal complexes) to promote these valuable transformations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all the products. 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.

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(16) One limitation of this system is that only alcohols bearing a small methyl substituent can be efficiently converted to the desired products. Much lower conversion (<10%) were obtained for alcohol substrates bearing bigger substituents than methyl. A more reactive catalytic system is being pursued to overcome this limitation.

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