Asymmetric Catalysis

DOI: 10.1002/ange.201304919

Rhodium-Catalyzed Dynamic Kinetic Asymmetric Transformations of Racemic Allenes by the [3+2] Annulation of Aryl Ketimines**

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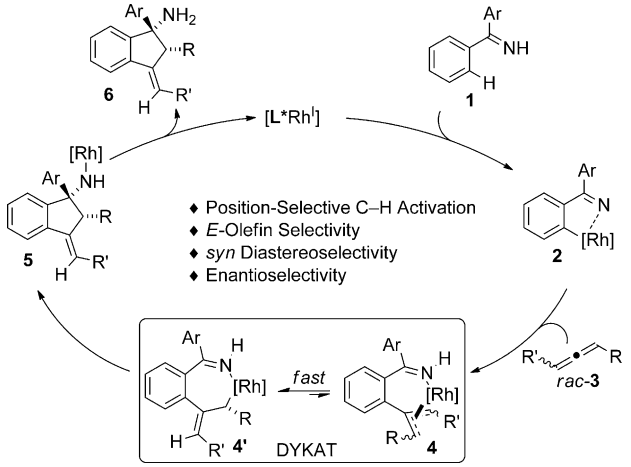
The vast occurrence of optically active amines in natural products and compounds with biological activity has prompted numerous efforts toward their synthesis.[1] Although a broad range of methods are available to access chiral amines, enantioselective carbon–hydrogen (C–H) bond functionalization[2] to access nitrogen-containing chiral building blocks remains largely underdeveloped. In accordance with our interest in developing synthetic tools for asymmetric C–H functionalization,[3] aiming to streamline the synthesis of complex molecules, we examined the potential of unprotected ketimines. We[4] and others[5] have shown that such unprotected ketimines are suitable directing groups for directed C–H bond functionalization. An attractive feature is the direct conversion of the directing group into highly versatile free primary amines by a [3+2] annulation during the course of the reaction. Both internal alkynes[4b,5a,c] and terminal allenes[4a,5b] were shown to be suitable coupling partners. Although a catalytic asymmetric version could be devised for alkynes,[4b] allenes were significantly more problematic. In particular, the process suffers from two important limitations that remain to be addressed. First, the reaction itself is restricted to terminal allenes. Furthermore, the described process is limited to a racemic [3+2] annulation and only one single example, with the most reactive ketimine, showed moderate enantioselectivity.[4a] Commonly, the axial chirality of 1,3-disubstituted or unsymmetrically substituted 1,1,3-trisubstituted allenes is exploited as a convenient handle to transfer the chiral information to the chiral center of the product.[6] A major drawback of this approach is the access to the required enantiopure allenes.[7] In contrast, a dynamic kinetic asymmetric transformation (DYKAT)[8] or a dynamic kinetic resolution (DKR),[9] in which both enantiomers converge and lead to the product enantiomer with an appropriate chiral catalyst, would allow the use of racemic allenes. Recent progress in the straightforward preparation of racemic allenes[10] would make such a process highly valuable, however only very scarce examples of DYKATs or DKRs with allenes have been reported thus far.[11]

Herein, we report a Rh^I-catalyzed DYKAT of racemic allenes, providing highly selective access to substituted indanylamine building blocks (Scheme 1). The reaction



Scheme 1. DYKAT in the [3+2] cycloaddition of aryl ketimines and racemic allenes.

envisioned is initiated by a C–H activation step directed by the unsubstituted ketimine **1** with a Rh^I catalyst. The positional selectivity of the activation is governed by kinetic C–H bond acidity, leading to cyclometalated intermediate **2**. In turn, coordination and migratory insertion of a racemic 1,3-disubstituted allene **3** potentially leads to eight different primary stereoisomers **4**.[12] We speculated that if the isomerization of these diastereomeric allyl rhodium intermediates would occur faster than the subsequent addition across the imine moiety, a DYKAT should become feasible. Isomerization could either occur by a σ-π-σ mechanism or a β-H elimination/readdition step.[13] Once this equilibration process reaches the proper allyl isomer **4′**, which favors the addition across the imine moiety, the 1,2-addition sets the diastereomeric and enantiomeric ratio of indanylamine **6**. Along the same lines, the double bond geometry is controlled.

The general feasibility of this hypothesis was initially evaluated with the unsymmetrical imine **1a** and racemic allene **3a** (Table 1). A brief survey of rhodium(I) catalysts revealed that cationic and chloride-counterion-bearing complexes were not competent, and therefore the robust [{Rh(cod)OH}$_2$] complex was used (entries 1–4). Binap (**L1**) already provides an excellent enantioselectivity of 97:3 e.r. and a high preference for the *E*-configured double bond

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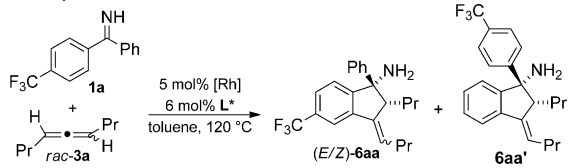
[**] This work was supported by the Swiss National Science Foundation (no 137666) and the European Research Council under the European Community's Seventh Framework Program (FP7 2007–2013)/ERC Grant agreement (257891). We thank Dr. R. Scopelliti for X-ray crystallographic analysis of **8jc** and the Takasago International Corporation for Segphos ligands.

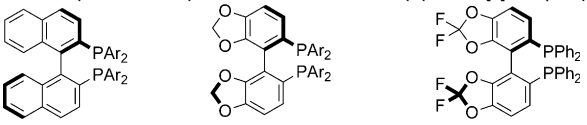
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201304919.

Table 1: Optimization studies of the DYKAT.[a]



Entry	[Rh]	L*	Yield [%][b]	**6aa**/**6aa'**[c]	*E*/*Z*[d]	e.r.[d]
1	$[\{Rh(cod)Cl\}_2]$	**L1**	<5	–	–	–
2	$[Rh(cod)_2]BF_4$	**L1**	0	–	–	–
3	$[\{Rh(C_2H_4)_2OAc\}_2]$	**L1**	77	6:1	13:1	97:3
4[e]	$[\{Rh(cod)OH\}_2]$	**L1**	87	4:1	13:1	97:3
5	$[\{Rh(cod)OH\}_2]$	**L1**	91	4:1	13:1	97:3
6	$[\{Rh(cod)OH\}_2]$	**L2**	86	6:1	13:1	97:3
7	$[\{Rh(cod)OH\}_2]$	**L3**	80	13:1	7:1	90:10
8	$[\{Rh(cod)OH\}_2]$	**L4**	80	5:1	11:1	99:1
9	$[\{Rh(cod)OH\}_2]$	**L5**	67	10:1	7:1	98:2
10	$[\{Rh(cod)OH\}_2]$	**L6**	82	13:1	2:1	92:8
11	$[\{Rh(cod)OH\}_2]$	**L7**	88	15:1	3:1	94:6

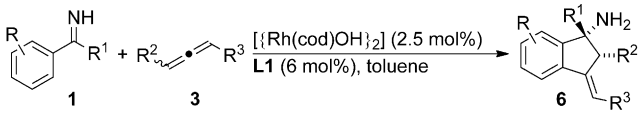
[a] Reaction conditions: **1a** (0.10 mmol), **3a** (0.12 mmol), [Rh] (5.00 μmol), **L*** (6.00 μmol), toluene (0.50 M), 120 °C, 12 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis on a chiral stationary phase. [e] **3a** (3 equiv).

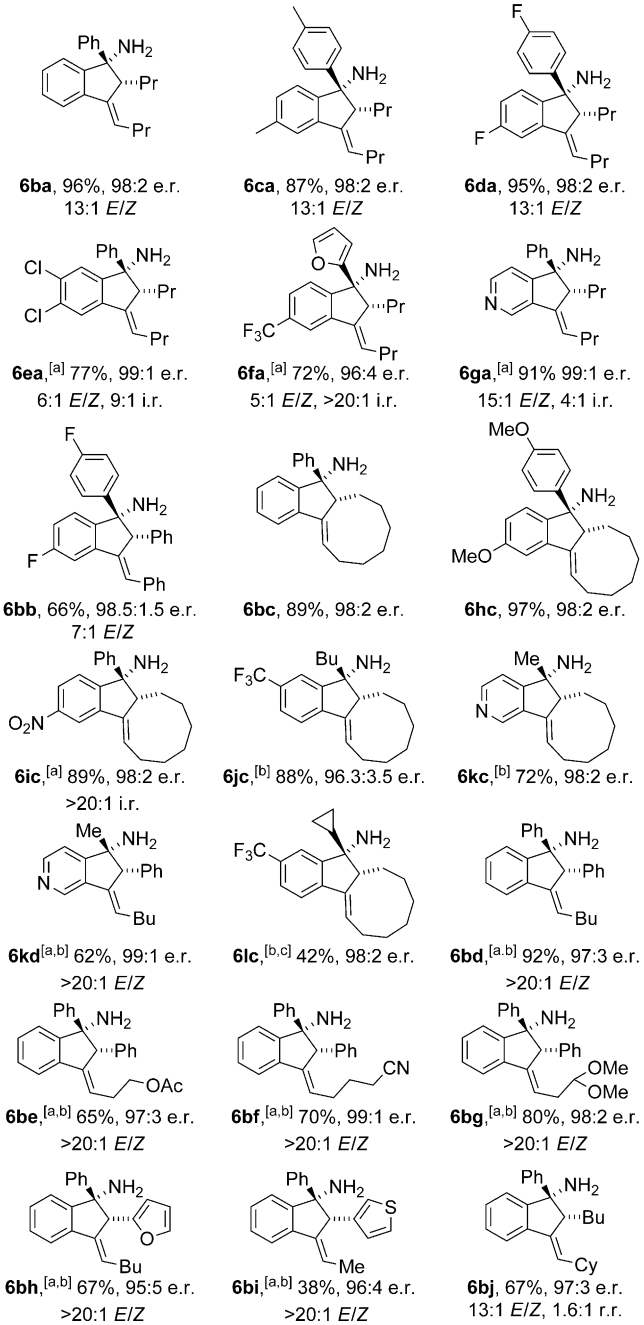


L1 (Ar = Ph)
L2 (Ar = 4-MeC_6H_4)
L3 (Ar = 3,5-MeC_6H_3)
L4 (Ar = Ph)
L5 (Ar = 3,5-MeC_6H_3)
L6 (Ar = 3,5-*t*Bu-4-$MeOC_6H_2$)
L7

(entry 4). We were pleased to observe no difference in yield or enantioselectivity when the reaction was carried out with 1.2 or 3 equivalents of allene **3a** (entries 4 and 5). This indicates a good equilibration mechanism of the racemic allene. However, the positional selectivity for the C–H bond activation between the phenyl substituent and the more electron-poor *p*-CF_3-phenyl group was only modest. A specific trend of the different selectivities and reactivities was observed and required fine-tuning of the ligand properties for good overall selectivity. For example, bulkier aryl groups on the ligand favor a higher regioselectivity (13:1) for the C–H activation step, but at the same time lower both the *E*/*Z*-control and the enantioselectivity (entries 5–7 and 8–10). Although Binap is a good choice for symmetrical diarylimines, DM-Segphos (**L5**) also provided an excellent enantioselectivity (98:2 e.r.), high regioselectivity for the C–H activation, and reasonable control of the double bond geometry (entry 9).

To explore the scope of the optimized process, we evaluated different substitution patterns on the arylimine portion (Scheme 2). Besides symmetrical diaryl ketimines, a variety of electronically different unsymmetrical diaryl ketimines were employed. The regioselectivities achieved in the C–H activation range from 4:1 (4-pyridyl vs. phenyl, **6ga**) to >20:1 (*p*-CF_3-phenyl vs. 2-furyl, **6fa**). Remarkably, the enantioselectivity is largely independent of the ketimine part, and aryl alkyl ketimines are well suited as substrates, giving the amines **6jc**, **6kc**, **6kd**, and **6lc** in excellent selectivities. Furthermore, electron-poor and coordinating heterocycles



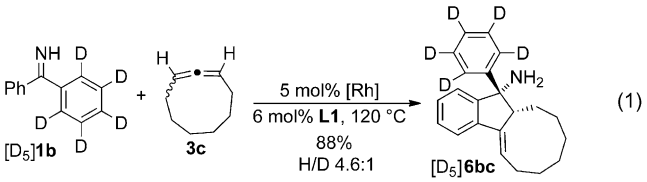


Scheme 2. Scope of the DYKAT cyclization process. Reaction conditions: **1** (0.10 mmol), **3** (1.2 equiv), $[\{Rh(cod)OH\}_2]$ (2.5 mol%), **L1** (6.0 mol%), toluene (0.50 M), 120 °C, 12 h, structure of the major product shown. [a] **L5** was used instead of **L1**. [b] **3** (3 equiv) was used. [c] Reaction at 100 °C. cod = 1,5-cyclooctadiene, i.r. = isomeric ratio of C–H activation, r.r. = regioisomeric ratio of allene incorporation.

such as pyridines do not interfere with the catalysis and are tolerated in this process. On the allene substrate part, we found that racemic cyclic allenes perform equally well. We next turned towards unsymmetrically 1,3-disubstituted

allenes. This substrate type adds another layer of complexity, as the allene can be incorporated in two different regioisomeric orientations. We found that the selectivity, and hence the equilibration, is strongly governed by electronic factors. As seen for products **6kd–6bi**, a benzylic allyl rhodium intermediate is largely favored over the alternative alkyl allyl intermediate. To a lesser extent, steric factors play a role; for example, **6bj** preferentially places the larger cyclohexyl group away from the congested amino group. In addition, the process is compatible with a range of common functional groups such as nitriles, esters, and acetals.

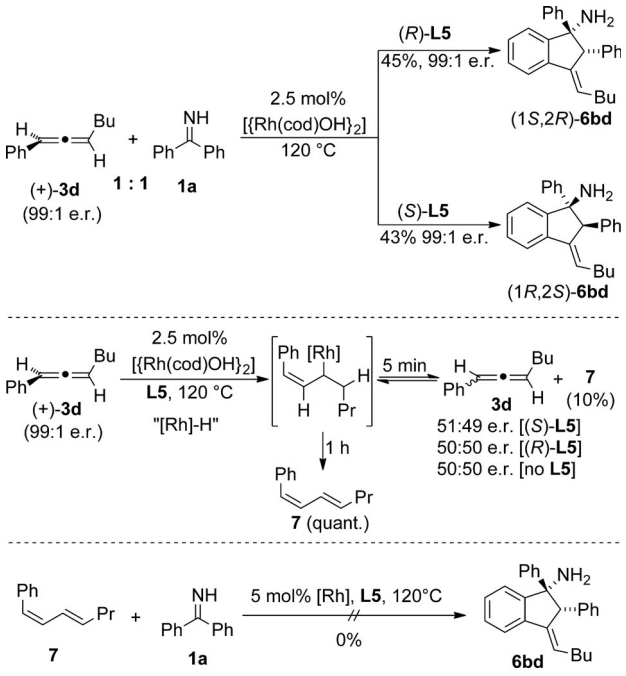
The selectivity of the C(sp^2)–H bond activation correlated with kinetic C–H bond acidity, and more electron-poor substrates are preferred. Deuteration experiments with substrate [D_5]**1b** showed a kinetic isotope effect of 4.6:1, which is typical for rate-limiting C–H bond activation [Eq. (1)].



(1)

To determine whether a dynamic equilibration or simply a kinetic resolution and decomposition of the mismatched isomer is the operating mechanism, we submitted an equimolar mixture of enantioenriched alkyl aryl allene **3d** and ketimine **1a** to both ligand enantiomers **L5** (Scheme 3).

In both cases, the configuration is fully controlled by the chiral ligand, and the axial chirality of the starting allene plays no role at all. The yields are almost identical, thus disproving

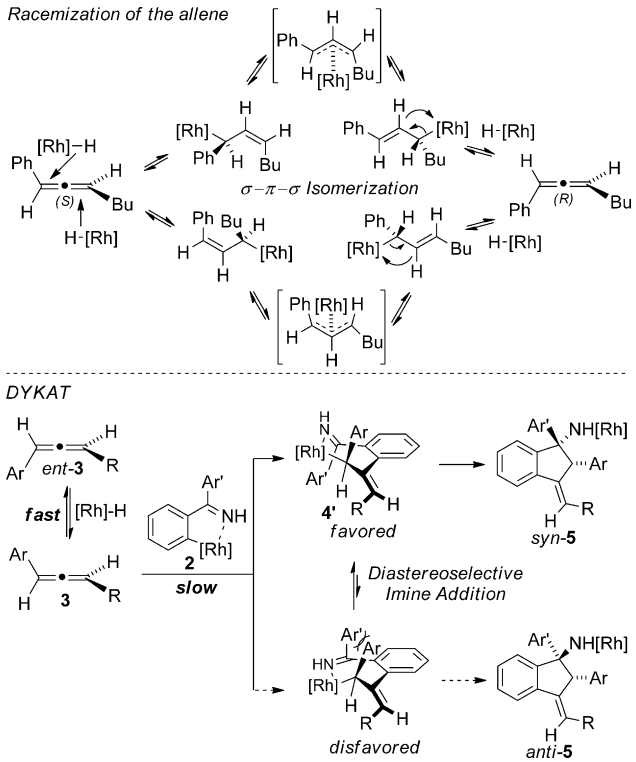


Scheme 3. Using allene **3a** to probe for DYKAT vs. kinetic resolution.

a simple kinetic resolution, which would operate by depleting the allene reservoir of the matching enantiomer. Furthermore, these results demonstrate the need for an excess of allene to ensure high yields, as some decomposition occurs during the reaction course. Submitting enantioenriched allene **3d** to the reaction conditions in the absence of the imine substrate results in complete racemization and some minor isomerization to diene **7** within 5 min.[14] The racemization occurs with and without **L5**, and no difference in racemization rate was detected with the different enantiomers of **L5**.[15] In one hour, complete conversion into the (*E*,*Z*)-diene **7** occurs. In turn, diene **7** is not a competent substrate for the [3+2] addition. The racemization and isomerization is induced by a rhodium hydride species which is generated directly from [{Rh(cod)OH}$_2$] as shown by Baba and co-workers.[16] In the presence of the ketimine, this isomerization and the racemization were found to be much slower. We attribute this to a rapid displacement of cod by the imine substrate before substantial amounts of the rhodium hydride species can be generated.[15] In contrast, bis(alkyl)-substituted allenes are perfectly stable under the reaction conditions (with and without ketimine) and do not isomerize to the corresponding dienes. Hence they require just a slight excess of allene (1.2 equiv) for complete conversion. With experimental evidence for the fast racemization of the allenes, we speculate that complex **2** reacts selectively with the matching allene enantiomer. As the racemization rate is significantly faster than the addition reaction, the concentration of the matching allene is sufficiently high throughout the reaction. The mismatched enantiomer is rapidly and constantly racemized. The racemization is initiated by a *syn* hydrorhodation leading to four possible σ-allyl complexes (Scheme 4).[14] Formation of the most stable *anti*-π-allyl complexes and subsequent isomerization gives the respective other σ-allyl complexes. *Syn* elimination provides the opposite allene enantiomer. For the [3+2]-annulation step, complex **2** selectively carborhodates the matching allene enantiomer, leading to the more-stable benzylic σ-bound allyl rhodium species **4′**. In principle, a non-specific carborhodation of both allene enantiomers and subsequent equilibration of intermediate **4** would be an alternative pathway to account for the DYKAT. Although this could still be viable for C_2-symmetric allenes, owing to a simple σ-π-σ isomerization, an isomerization of unsymmetric allenes is significantly less probable.[17] The observed diastereoselectivity of the cyclization can be rationalized by comparing the two possible orientations for the imine addition. Placing the allene Ar substituent and the Ar′ group of the imine away from each other minimizes steric interactions and provides *syn* product **5**, which is exclusively observed. This orientation is governed by the stereogenic allyl–rhodium center and explains the surprisingly high enantioselectivity found with small alkyl aryl imines.

The absolute configuration of the prepared amines **6** was assigned as 1*R*,2*R*, as determined by X-ray crystallographic analysis of the *p*-Br-benzoylated derivative **8jc** (Figure 1).[18]

In summary, we have reported a rhodium(I)-catalyzed DYKAT of racemic allenes. The described process offers excellent control of the positional selectivity of the C–H bond activation governed by kinetic C–H bond acidity, the double-



Scheme 4. Mechanistic hypothesis for the allene racemization, DYKAT, and the diastereoselectivity of the addition.

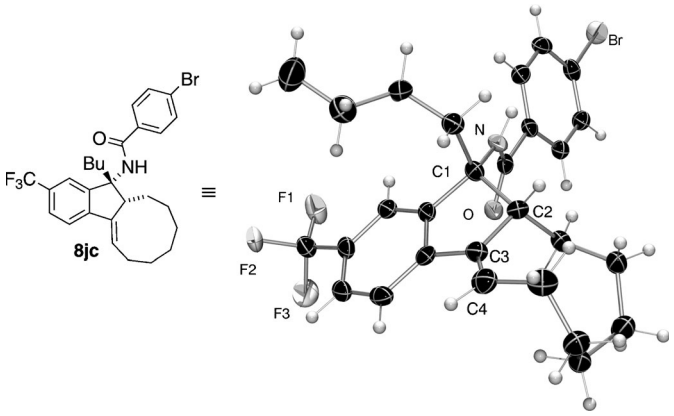


Figure 1. ORTEP representation of **8jc**. Ellipsoids set at 50%.

bond geometry and the diastereo- and enantioselectivity of the allene incorporation. The use of readily accessible racemic allenes and unprotected ketimines allows for the build-up of molecular complexity, giving synthetically valuable and heavily substituted indenylamines. In addition, the rapid rhodium-catalyzed isomerization discovered should pave the way for further DYKAT applications with allenes.

Received: June 7, 2013
Revised: July 12, 2013
Published online: August 16, 2013

Keywords: allenes · asymmetric catalysis · C–H activation · DYKAT · rhodium

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[17] See the Supporting Information for details on the alternative isomerization pathways.

[18] CCDC 949868 (**8jc**) contains 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.