Asymmetric Catalysis

International Edition: DOI: 10.1002/anie.201610500
German Edition: DOI: 10.1002/ange.201610500

Rhodium-Catalyzed Asymmetric Synthesis of β-Branched Amides

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Abstract: *A general asymmetric route for the one-step synthesis of chiral β-branched amides is reported through the highly enantioselective isomerization of allylamines, followed by enamine exchange, and subsequent oxidation. The enamine exchange allows for a rapid and modular synthesis of various amides, including challenging β-diaryl and β-cyclic.*

Enantiopure β-branched amides are common motifs in natural products and biologically active molecules[1] (Figure 1) and are useful synthetic intermediates for the

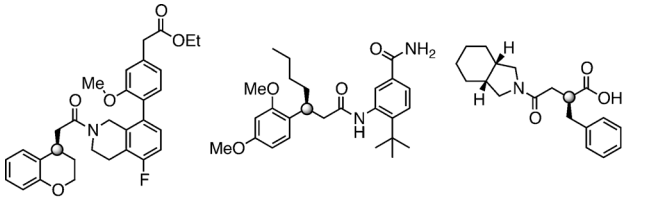
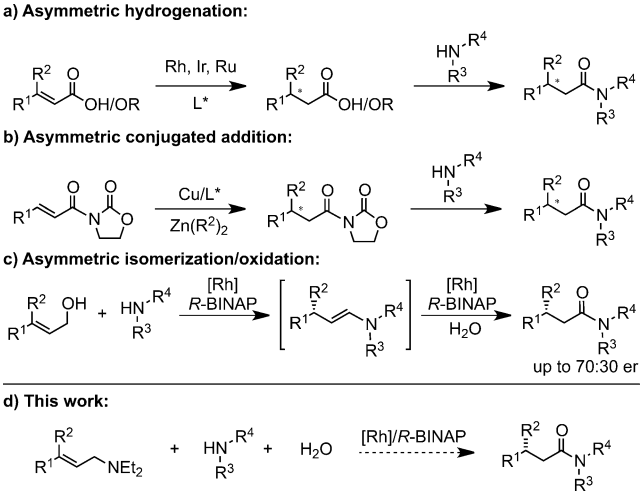


Figure 1. Biologically active compounds containing chiral β-branched amides.

construction of γ-branched chiral amines.[2] However, examples of the direct asymmetric synthesis of chiral β-branched amides are rare. Although asymmetric hydrogenation or conjugate addition of α,β-unsaturated carbonyls are common strategies toward β-stereocenters, α,β-unsaturated amides intrinsically display low reactivity.[3] Only a few examples of unsaturated acyclic amides have been documented, including Co-catalyzed asymmetric reduction[4] and Rh-catalyzed conjugate addition.[5] For a general and modular synthesis of enantiopure β-branched amides, a multistep sequence is often required via carboxylic acid intermediates (Scheme 1).[1c] For example, asymmetric hydrogenation of β,β-disubstituted unsaturated acrylic acid or ester has been extensively studied to reach high conversion and excellent enantioselectivity via Rh, Ir, and Ru catalysis (Scheme 1a).[6] The same chiral acid intermediate could be prepared through a copper-catalyzed asymmetric 1,4-addition of an alkylzinc to a unsaturated *N*-acyloxazolidione followed by hydrolysis (Scheme 1b).[7] For the synthesis of the desired amide products, stoichiometric



Scheme 1. Enantioselective β-branched amide syntheses.

coupling reagents are often required which leads to poor atom economy.[8]

Considering the dearth of approaches for the direct asymmetric synthesis of chiral β-branched amides, we proposed that allylic alcohols could serve as a chiral aldehyde precursor, which upon asymmetric isomerization and subsequent oxidative amidation with an amine, affords the desired product in a single step (Scheme 1c). We recently reported a cationic Rh/BINAP complex as an effective catalyst for this transformation, converting primary and secondary amines as well as anilines into amides.[9] However, only moderate er was observed when using trisubstituted allylic alcohols as substrates.[10] As an enamine intermediate is formed over the course of the reaction, we hypothesized that utilizing Noyori's asymmetric isomerization of allyl amines, a highly enantioselective process and the key step in the Takasago Process, could allow for the formation of identical intermediates with improved enantioselectivity.[11] To avoid preinstallation of the amine functionality on the substrate, we further proposed a domino process: enantioselective isomerization of an allylic amine, enamine exchange with an external amine nucleophile, and oxidation of enamine to afford enantiopure β-branched amides in a single step (Scheme 1d).

The key challenge for this tandem process is identifying an appropriate allyl amine precursor, as it must: isomerize with high enantioselectivity, afford an enamine (**ii**) which is slow to oxidize and instead undergo enamine exchange with an external amine nucleophile to afford the desired intermediate (**i**) (Scheme 2). We hypothesized that acyclic dialkyl amines could serve as precursors as they are good substrates in related Rh-catalyzed asymmetric isomerization reactions[11] and are not reactive in the oxidative amidation of allyl alcohols.[9] Several allylic dialkyl amines(**1a**–**1d**) were

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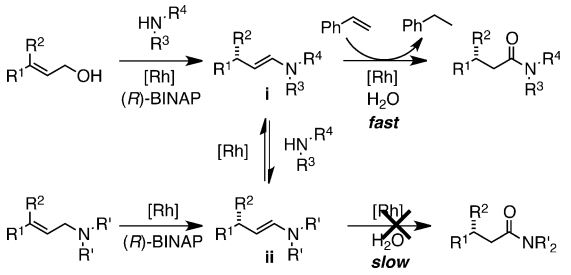
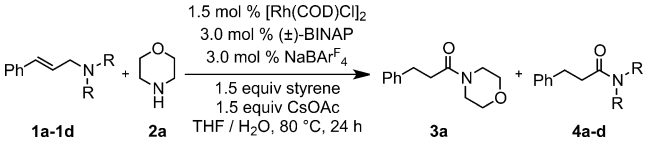
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201610500.



Scheme 2. Proposed reaction pathway.

screened for this tandem process (Table 1). Under slightly modified conditions from the allylic alcohol amidation,[12] the desired morpholine amide (**3a**) was formed in moderate yields from all the allylic amine precursors. Only cinnamyl dimethylamine (**1a**) provided 9% byproduct **4a**, consistent with dimethyl amine being an effective nucleophile in our allylic alcohol amidation.[9] We chose to further optimize this reaction with cinnamyl diethylamine (**1b**), as it forms a low molecular weight byproduct ($NHEt_2$) which is easily removed.

Table 1: Rhodium-catalyzed allylic dialkylamine amidation.[a]



Entry	R	Yield of **3a** [%][b]	Yield of **4a–4d** [%][c]
1	Me	64	9
2	Et	77	<1
3	*i*-Pr	71	<1
4	Bn	74	<1

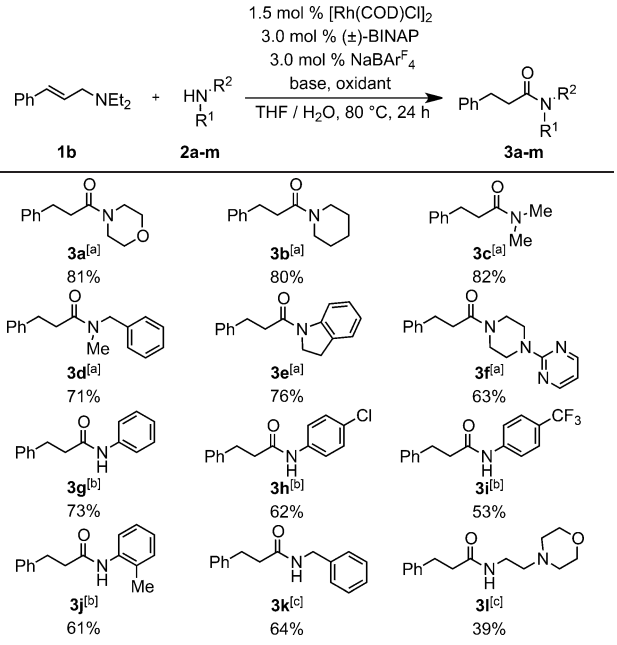
[a] General reaction conditions: cinnamyl dialkylamine (**1**) (0.12 mmol, 1.0 equiv), morpholine (**2a**) (1.5 equiv), CsOAc (1.5 equiv), styrene (1.5 equiv), THF (1.2 M), DI H_2O. [b] In situ yield determined by GC analysis. [c] In situ yield determined by NMR.

The further optimization of reaction conditions was elaborated in Tables S1–S6 (see Supporting Information): Cs_2CO_3 proved superior to CsOAc for secondary amine nucleophiles and only substoichiometric amount (20 mol%) is required (Tables S2 and S4). A variety of hydrogen acceptors were examined showing styrene to be superior, as it was reduced faster than the substrate (Table S3). Further, decreasing the equivalents of amine nucleophile (1.05 equiv) led to only slightly diminished yields (Table S2).

Slight modification of the reaction conditions was required for other amine nucleophiles. For less nucleophilic aniline derivatives, excess nucleophile (3.0 equiv) and increased base (0.9 equiv) were required to prevent unproductive reaction pathways (Table S5). With primary alkyl amine nucleophiles, a stronger base and higher temperature were essential, which presumably aid in the conversion of the less electrophilic imine intermediate to the hemiaminal intermediate. Additionally, acetone proved to be the better hydrogen acceptor, consistent with our allylic alcohol amidation (Table S6).[9]

With the optimized conditions in hand, the amine nucleophile scope was investigated (Table 2): cyclic amines such as piperidine (**2b**), indoline (**2e**), and 2-(piperazin-1-yl) pyrimidine (**2f**) and acyclic amines, including dimethyl amine

Table 2: Scope of amine nucleophiles.



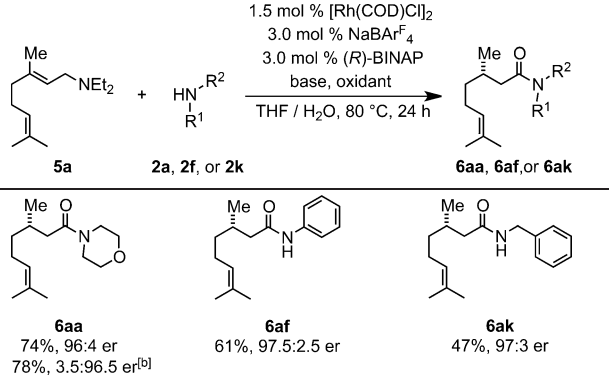
[a] Condition a: secondary amines (1.05 equiv), Cs_2CO_3 (20 mol%), styrene (1.5 equiv), THF/H_2O (1:0.2). [b] Condition b: anilines (3.0 equiv), Cs_2CO_3 (90 mol%), styrene (1.5 equiv), THF/H_2O (1:0.3). [c] Condition c: primary alkyl amine (1.0 equiv), KOH (2.5 equiv), acetone (1.0 equiv), THF/H_2O (1:1), 100°C.

(**2c**) and *N*-benzyl methyl amine (**2d**) all gave excellent yields of desired products. Moderate yields were obtained with aniline derivatives (**2g**–**2j**). Electron-deficient (**2i**) and sterically hindered anilines (**2j**) afford slightly diminished yields. Primary amines are relatively challenging nucleophiles for this reaction and **3k** and **3l** were obtained in 64% and 39%, respectively. Unsurprisingly, diethyl and dibenzyl amines showed no reactivity under optimized conditions, consistent with results in Table 1.

The enantioselectivity of this transformation was explored under optimized conditions with different amine nucleophiles (Table 3). Excellent enantioselectivities (>96:4 er) were observed in the asymmetric oxidative amidation of (*E*)-geranyl diethyl amine with morpholine, aniline, and benzyl amine, affording **6aa**, **6af**, and **6ak** in fair to excellent yields. Using either (*S*)-BINAP or the (*Z*)-allyl diethylamine affords the opposite enantiomer in identically excellent enantioselectivity.[13]

Focusing our efforts on substrates not previously shown in the Noyori isomerization, the scope of prochiral allylamines was next explored (Table 4). A variety of substrates were transformed to the corresponding β-branched amides with high enantioselectivities in moderate to very good yields.

Table 3: Enantioselective isomerization/amidation of (*E*)-geranyl diethyl amine.[a]



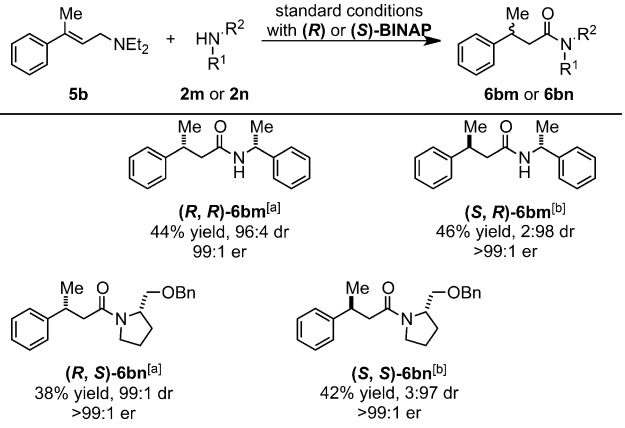
[a] For conditions see Table 2.[14] Isolated yield, average of two runs. Absolute configuration is assigned by analogy to **6oa** (see below). [b] With (*S*)-BINAP.

Various 3,3-aryl,alkyl allylic diethylamines were investigated (**5b**–**5h**); stereocenters bearing both small (Me, Et) and large (*i*Pr) substituents uniformly give excellent enantiomeric ratios (**6ba**-**6da**).[16] Aryl halides were tolerated under the optimized conditions, although some protodebromination product was observed from aryl bromides (**6gg**). When β-dialkyl allylic diethylamines (**5i**–**5l**) were exposed to the reaction conditions, chiral amides bearing a dialkyl stereocenter were obtained with excellent enantioselectivity, even with minimally differentiated substituents (**6la**, *n*Bu vs. *n*Pent).

Additionally, 3,3-diaryl allylic diethylamines also undergo this asymmetric isomerization/oxidation reaction. Substrates bearing electron-rich (**6ma**) and electron-poor (**6na**) aryl substituents afforded good yields and enantiomeric ratios. Heterocycles such as thiophene were tolerated and compatible with both secondary cyclic (**6oa**) and acyclic (**6od**) amine nucleophiles. Further, a chroman-derived β-cyclic substrate (**5p**) afforded the chiral amide product with excellent enanotioselectivity, demonstrating an improvement over other approaches, for example, chiral resolution.[16]

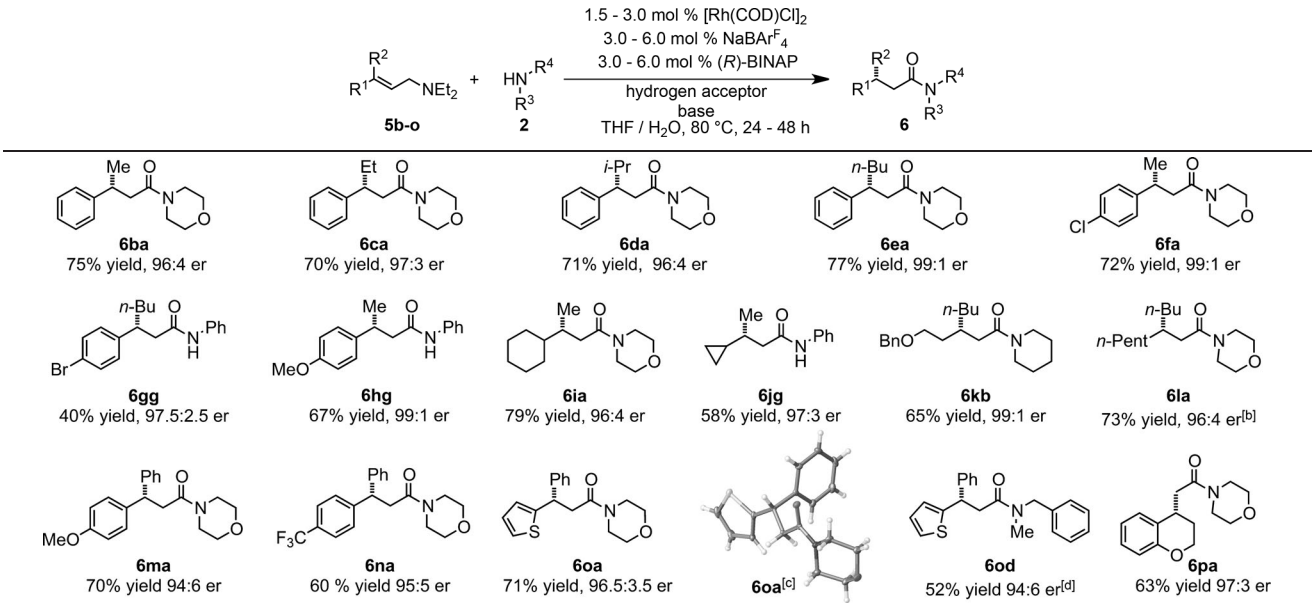
The diastereoselectivity of this reaction was investigated with enantiopure amine nucleophiles (Table 5). When chiral α-branched amines **2m** and **2n** were used as nucleophiles, **6bm** and **6bn** were formed in high er (>99:1) and dr (>96:4). Further, both the enantiomer of ligand, (*R*)- or (*S*)-BINAP, and the enantiomer of amine employed dictate which diastereomer is formed. This indicates both that the stereocenter α to the amine are unepimerized under the reaction conditions, even with the relatively activated chiral benzylic

Table 5: Diastereoselectivity with enantiopure amine nucleophiles.[14]



[a] with (*R*)-BINAP. [b] with (*S*)-BINAP.

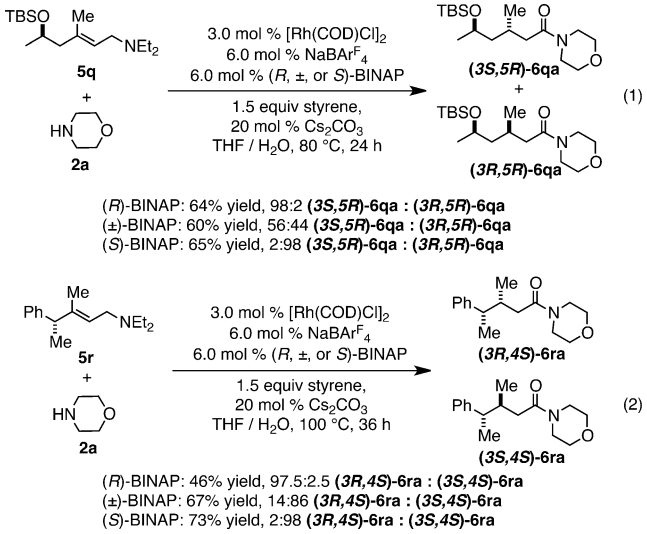
Table 4: Scope of one-step asymmetric isomerization/amidation of allylic amines.[a]



[a] For conditions see Table 2.[14] Isolated yield, average of two runs. [b] Determined from the dr of transamidation product from **6la**.[14] [c] Absolute configuration of **6oa** was determined by X-ray crystallography.[14] [d] 96:4 *E*/*Z* ratio of starting material.

amine (**2m**), and that it has no effect on the selectivity of the isomerization reaction.

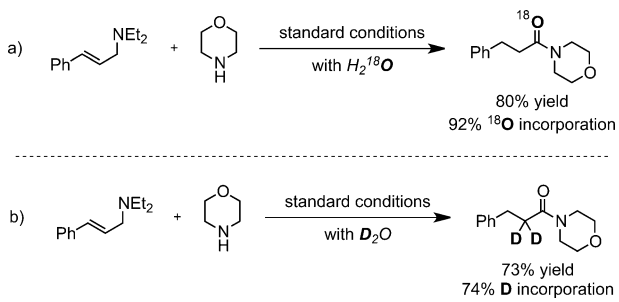
Next the isomerization of allylic amine with proximal stereocenters was examined (Scheme 3). Interestingly, the



Scheme 3. Diastereoselectivity with enantiopure allyl amines.[14]

diastereoselecitivity of the isomerization of **5q** and **5r** with (±)-BINAP favored the formation of (*3S,5R*)-**6qa** (56:44 dr) and (*3S,4S*)-**6ra** (14:85 dr), respectively, where the closer stereocenter in **5r** has a greater effect on the diastereoselectivity of the reaction. Excitingly, both **5q** and **5r** undergo the Rh-catalyzed isomerization/oxidation to afford desired products with excellent diastereoselectivities (>97.5:2.5) when enantioenriched ligands are employed. The isomerization reaction proved to be ligand-controlled, as the mismatched combination of (*R*)-BINAP and **5r** decreased the yield of (3*R*,4*S*)-**6ra**, rather than the diastereoselectivity.

As shown in Scheme 4, isotope labelling studies were carried out using $H_2{}^{18}O$ and D_2O respectively. The $H_2{}^{18}O$ labelling study (Scheme 4a) confirms that the oxygen in the product originates from the water. Similarly, deuterium incorporation at the α-position of the amide was observed (Scheme 4b), as it was in the allylic alcohol amidation,[9] supporting the reversible formation of enamine intermediate **i** (Scheme 2).



Scheme 4. Isotope labelling study.

In conclusion, we have developed a Rh-catalyzed one-step synthesis of chiral β-branched amides. This method allows for the installation of a stereocenter and amide functionality in a single step under mild conditions. Excellent enantio- and diastereoselectivity was observed for a variety of allylic amine substrates and amine nucleophiles. The expansion of this methodology to other types of stereocenters and nucleophiles currently is under investigation.

Acknowledgements

We thank the University of Illinois, ACS PRF (54007-DNI1), and NSF CAREER (0332333) for their generous support. S.D.L. and J.D.M. are grateful to the NSF GRFP (DGE-1144245).

Keywords: amidation · asymmetric isomerization · β-branched amides

[1] a) N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Educ.* **2010**, *87*, 1348 – 1349; b) H. Aissaoui, C. Boss, S. Richard-Bildstein, R. Siegrist, *PTC Int. Appl.* **2013**, WO 2013093842; c) M. Murakami, K. Kobayashi, K. Hirai, *Chem. Pharm. Bull.* **2000**, *48*, 1567 – 1569; d) T. Yamaguchi, T. Yanagi, H. Hokari, Y. Mukaiyama, T. Kamijo, I. Yamamoto, *Chem. Pharm. Bull.* **1997**, *45*, 1518 – 1520.

[2] a) T. C. Nugent, *Chiral Amine Synthesis*: *Methods*, *Developments and Applications*, Wiley-VCH, Weinheim, **2010**; b) M. Shibuya, T. Taniguchi, M. Takahashi, K. Ogasawara, *Tetrahedron Lett.* **2002**, *43*, 4145 – 4147.

[3] For recent reviews, see: a) S. Khumsubdee, K. Burgess, *ACS Catal.* **2013**, *3*, 237 – 249; b) J. J. Verendel, O. Pamies, M. Dieguez, P. G. Andersson, *Chem. Rev.* **2014**, *114*, 2130 – 2169; c) K. M. Byrd, *Beilstein J. Org. Chem.* **2015**, *11*, 530 – 562.

[4] P. von Matt, A. Pfaltz, *Tetrahedron: Asymmetry* **1991**, *2*, 691 – 700.

[5] a) S. Sakuma, N. Miyaura, *J. Org. Chem.* **2001**, *66*, 8944 – 8946; b) C. Defieber, J.-F. Paquin, S. Serna, E. M. Carreira, *Org. Lett.* **2004**, *6*, 3873 – 3876.

[6] Ref. [3a,b] and references therein.

[7] A. W. Hird, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2003**, *42*, 1276 – 1279; *Angew. Chem.* **2003**, *115*, 1314 – 1317.

[8] a) I. Coin, M. Beyermann, M. Bienert, *Nat. Protoc.* **2007**, *2*, 3247 – 3256; b) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411 – 420.

[9] Z. Wu, K. L. Hull, *Chem. Sci.* **2016**, *7*, 969 – 975.

[10] Rh-catalyzed enantioselective isomerization of allylic alcohols: a) K. Tanaka, G. C. Fu, *J. Org. Chem.* **2001**, *66*, 8177 – 8186; b) K. Tanaka, S. Qiao, M. Tobisu, M. M.-C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 9870 – 9871.

[11] a) K. Tani, T. Yamagata, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, S. Otsuka, *J. Am. Chem. Soc.* **1984**, *106*, 5208 – 5217; b) S.-I. Inoue, H. Takaya, K. Tani, S. Otsuka, T. Satao, R. Noyori, *J. Am. Chem. Soc.* **1990**, *112*, 4897 – 4905.

[12] Initial counter ion screens show $BAr_4{}^{F-}$ gives much higher reactivity for allylic amine isomerization. See Table S1 for details.

[13] (*Z*)-Geranyl diethyl amine combined with (*R*)-BINAP under optimized conditions afforded (*R*)-**6aa** in 78% yield and 3.5:96.5 er.
[14] See Supporting Information for details.
[15] a) L. Mantilli, D. Gerard, S. Torche, C. Besnard, C. Mazet, *Angew. Chem. Int. Ed.* **2009**, *48*, 5143 – 5147; *Angew. Chem.* **2009**, *121*, 5245 – 5249; b) N. Arai, K. Sato, K. Azuma, T. Ohkuma, *Angew. Chem. Int. Ed.* **2013**, *52*, 7500 – 7504; *Angew. Chem.* **2013**, *125*, 7648 – 7652.
[16] For examples of other asymmetric allylic isomerizations see: P. Wickens, L.-D. Cantin, C.-Y. Chuang, M. Dai, M. F. Hentemann, E. Kumarasinghe, S. X. Liang, D. B. Lowe, T. E. Shelekhin, Y. Wang, C. Zhang, H.-J. Zhang, Q. Zhao, WO2004011446 A1, Feb 5, **2004**.

Manuscript received: October 26, 2016
Final Article published: ■■ ■■, ■■■■

Communications

Asymmetric Catalysis

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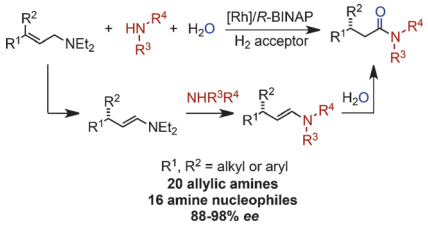
Rhodium-Catalyzed Asymmetric Synthesis of β-Branched Amides



A domino process: A Rh^{I}/chiral BINAP catalysis is reported for the one-step modular synthesis of chiral β-branched amides with various amine nucleophiles. β-dialkyl, β-diaryl, and β-alkylaryl stereocenters are established under identical conditions with excellent enantio- and diastereoselectivity in a ligand-controlled manner.