A Journal of the Gesellschaft Deutscher Chemiker

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Title: Catalytic Enantioselective Intermolecular Benzylic C(sp3)—H Amination

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201902882
Angew. Chem. 10.1002/ange.201902882

Link to VoR: http://dx.doi.org/10.1002/anie.201902882
http://dx.doi.org/10.1002/ange.201902882

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Catalytic Enantioselective Intermolecular Benzylic C(sp^3)—H Amination

Ali Nasrallah, Vincent Boquet, Alexandra Hecker, Pascal Retailleau, Benjamin Darses, and Philippe Dauban[*]

Dedicated to Paul Müller on the occasion of his 80th birthday

Abstract: A practical general method for asymmetric intermolecular benzylic C(sp^3)—H amination has been developed by combining the pentafluorobenzyl sulfamate PfbsNH$_2$ with the chiral rhodium(II) catalyst Rh$_2$(*S*-tfptad)$_4$. Various substrates can be used as limiting components and converted to benzylic amines with excellent yields and high levels of enantioselectivity. Additional key features for the reaction are the low catalyst loading and the ability to remove the Pfbs group under mild conditions to give NH-free benzylic amines.

Chiral benzylic amines are useful nitrogen compounds that can be found in the structure of pharmaceuticals (Rivastigmine, Cinacalcet), agrochemicals (Indaziflam), chiral auxiliaries and ligands for asymmetric synthesis (Figure 1).[1] They are also new motifs that have been incorporated in recent leads to improve their "drug-likeness".[2] Such a key role for these nitrogen-containing molecules has translated to the design of catalytic asymmetric C—N bond forming reactions.[3]

Catalytic enantioselective C(sp^3)—H functionalization reactions have recently emerged as efficient tools for the synthesis of optically pure organic compounds. The asymmetric conversion of a C—H bond is a great challenge, and though this field of investigation is still in its infancy, significant achievements have been reported.[4] The prevalence of nitrogen in life sciences, in this context, has motivated the search for conditions to develop catalytic C(sp^3)—H amination reactions.[5] Notable progress has been made through the development of catalytic nitrene C(sp^3)—H insertions.[6] The design of chiral transition metal complexes, then, has led to the discovery of catalytic asymmetric C(sp^3)—H amination reactions that mostly involve nitrenes generated from azides, or in the presence of iodine(III) oxidants.[7]

Efficient intramolecular processes have been reported in the presence of chiral Rh, Ru, Ir, and Co complexes or mutated P450 enzymes. The internal delivery of a tethered nitrene generally allows the reaction to proceed with excellent yields and enantioselectivities either from sulfamates[8] or sulfonyl azides.[9] By contrast, the corresponding intermolecular reaction has been less explored. Following the pioneering study of Müller with chiral rhodium(II) complexes,[10] Hashimoto[11] and Davies[12] have

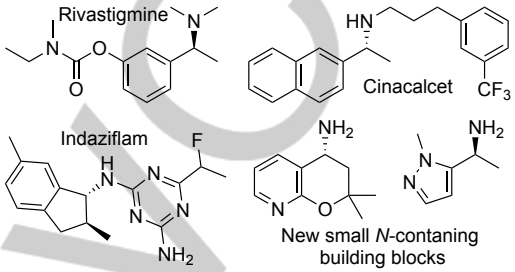
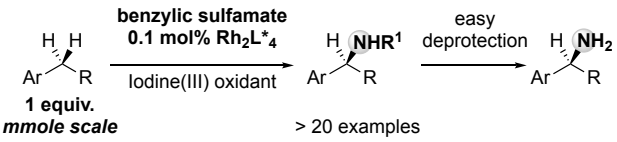


Figure 1. Chiral benzylic amines in life sciences.

reported new catalysts for the asymmetric benzylic C(sp^3)—H amination. The latter, however, proceed under substrate-excess conditions and, in most cases, with limited enantiocontrol.[13] Inspired by the Rh$_2$(esp)$_2$ complex,[14] Bach has developed a supramolecular approach to address this issue,[15] but again, the yields and enantiomeric excesses are moderate while the scope is limited to 3-benzylquinolones. In this context, the use of azides in combination with a Ru-salen complex[16] or an engineered iron-haem enzyme[17] has afforded relevant solutions. However, there is still room for improvement as these processes have also their limitations such as the need of an excess of substrate, a high catalyst loading or low yields in some cases.

In this manuscript, we, thus, wish to report a catalytic asymmetric intermolecular C(sp^3)—H amination that applies to a wide range of benzylic substrates (Scheme 1). The reaction, which relies on the design of a new benzylic sulfamate as a nitrene precursor and chiral rhodium(II) complexes, occurs under stoichiometric conditions on a mmole scale and with a low catalyst loading.



Scheme 1. High yielding enantioselective intermolecular C(sp^3)—H amination.

Our studies have started with the commercially available chiral complex dirhodium(II) tetrakis[*N*-tetrafluorophtaloyl-(*S*)-*tert*-leucinate] (Rh$_2$(*S*-tfpttl)$_4$) **4a**. The reaction of ethylbenzene **1a**, used as the limiting reagent, with the benzylic sulfamate **3a** proceeds in 73% yield and with an enantiomeric ratio (e.r.) of 4:1 (entry 1, Table 1). This preliminary result, thus, led us to consider benzylic sulfamates as highly reactive nitrene sources. These sulfamates have been rarely considered as nitrene precursors so

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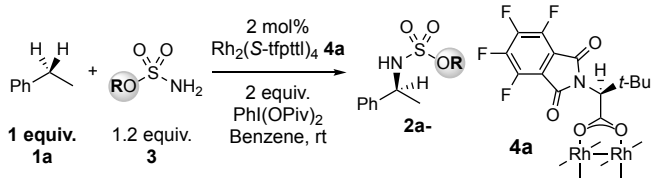
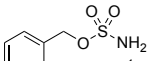
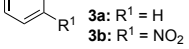
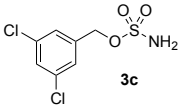
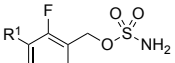
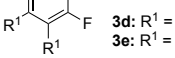
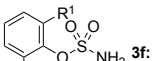
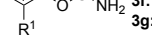
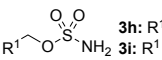
10.1002/anie.201902882

far,[18] and are easily accessible from the corresponding alcohols following reaction with sulfamoyl chloride.[19]

Table 1. Screening of sulfamates with Rh_2(*S*-tfpttl)$_4$.[a]



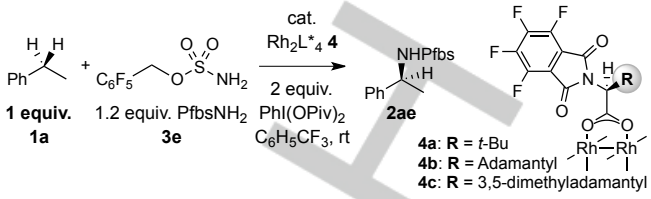
Entry	Sulfamate	Yields of **2a-** [%][b]	e.r.[c]
1		**2aa:** 73	80:20
2	 **3a:** R^1 = H **3b:** R^1 = NO_2	**2ab:** 73	75:25
3	 **3c**	**2ac:** 86	80:20
4[d]		**2ad:** 95	80:20
5[d]	 **3d:** R^1 = H **3e:** R^1 = F	**2ae:** 97	81:19
6		**2af:** 34	69:31
7	 **3f:** R^1 = H **3g:** R^1 = F	**2ag:** 39	77:23
8[e]	 **3h:** R^1 = CCl_3	**2ah:** 75	81:19
9	**3i:** R^1 = CF_2CF_3	**2ai:** 80	78:22

[a] Reaction conditions: A mixture of **1a** (0.10 mmol), **3** (0.12 mmol), and catalyst **4a** (2 mol%) in benzene (1 mL) was stirred at rt for 16 h. [b] Isolated yields after flash chromatography. [c] Determined by chiral HPLC (Daicel Chiralpak IC-5). [d] Reaction performed in triplicate. [e] Reaction performed in duplicate.

Various sulfamates were evaluated for the amination of ethylbenzene catalyzed by **4a**. The screening confirmed the high reactivity of benzylic sulfamoyl nitrenes, the highest yields being obtained in the presence of halogen-substituted derivatives (entries 3-5). Gratifyingly, the pentafluorobenzyl sulfamate ($PfbsNH_2$) **3e** led us to isolate the expected product **2ae** with an excellent yield of 97% and an e.r. of 81:19 and was chosen as the nitrene precursor for the subsequent studies.[20] The screening also included sulfamates **3f-i** previously designed by Du Bois for intermolecular C(sp^3)—H amination (entries 6-9).[21] However, under these conditions, all proved to react less efficiently.

Modification of the reaction parameters, then, led us to evaluate the influence of the solvent on the yield and enantioselectivity. We, thus, found that the best result was provided by the use of trifluorotoluene, which afforded **2ae** with a yield of 92% and an e.r. of 82:18 (See Table S1, supporting information). In parallel, various dirhodium(II) complexes were screened thereby revealing the critical influence of the perfluorinated phthaloyl protecting group on the enantioselectivity (See Scheme S1, supporting information).[22] We, then, decided to study the influence of the amino acid side chain on the course of the reaction (Table 2).

Table 2. Screening of the dirhodium(II) complexes.[a]



Entry	**R** (L) (mol %)	Yields of **2ae** [%][b]	e.r.[c]
1	**Me** (*S*-tfpta) (2)	33	-
2	***i*-Pr** (*S*-tfptv) (2)	59	78:22
3	**Bn** (*S*-tfptpa) (2)	-	-
4	***t*-Bu** (*S*-tfpttl) (2)	97	82:18
5[d]	***t*-Bu** (*S*-tfpttl) (2)	82	87:13
6	**Adamantyl** (*S*-tfptad) (2)	92	84:16
7[d]	**Adamantyl** (*S*-tfptad) (2)	90	89:11
8[d]	**Adamantyl** (*S*-tfptad) (1)	90	89:11
9[d]	**Adamantyl** (*S*-tfptad) (0.1)	82	91:9
10	**3,5-Dimethyladamantyl** (2)	92	82:18
11[d]	**3,5-Dimethyladamantyl** (2)	80	86:14

[a] Reaction conditions unless otherwise stated: A mixture of **1a** (0.10 mmol), **3e** (0.12 mmol), and catalyst **4** (2 mol%) in trifluorotoluene (1 mL) was stirred at rt for 16 h. [b] Isolated yields after flash chromatography. [c] Determined by chiral HPLC (Daicel Chiralpak IA-5 or IC-5). [d] Reaction performed at -10 °C.

The screening revealed that the enantioselectivity increases with ligands having bulkier side chains. Thus, switching from a methyl to a *t*-butyl substituent allowed for improving both the yield and the e.r. (entries 1-4). This observation led us to prepare sterically more demanding ligands having either an adamantyl or a 3,5-dimethyladamantyl side chain.[23] In both cases, excellent yields were obtained, however, the Rh_2(*S*-tfptad)$_4$ **4b** proved to be slightly more efficient in terms of enantioselectivity (entries 6 and 10). Further improvement was achieved by running the reaction at -10 °C (entries 5, 7 and 11) with the Rh_2(*S*-tfptad)$_4$ complex **4b** affording again the highest e.r..[24] Finally, the same levels of reactivity and selectivity were maintained with catalyst loadings as low as 1 mol% or 0.1 mol% (entries 8 and 9). The conditions of entries 8 and 9, therefore, were chosen to investigate the scope of the asymmetric benzylic C(sp^3)—H amination (Scheme 2).[25]

The optimal conditions have been applied to a wide range of substrates. The use of 1 mol% of complex **4b** led to isolate the corresponding products with yields of up to 99% and e.r. of up to 92:8. On the other hand, the reactions involving 0.1 mol% of **4b** were performed on the mmole scale and generally led to slightly improve the e.r. of up to 94.5:5.5,[26,27] though the yields, in some cases, were reduced by roughly 5-15%.

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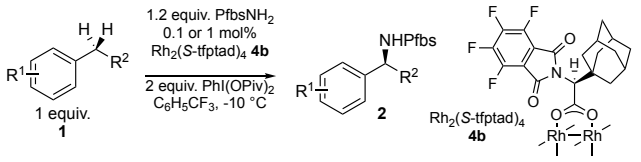


	0.1 mol% 4b	1 mol% 4b
2ae: R^1 = H	82% - *e.r. 91:9*	90% - *e.r. 89:11*
2be: R^1 = OMe	83% - *e.r. 91:9*	93% - *e.r. 89:11*
2ce: R^1 = Cl	65% - *e.r. 90:10*	80% - *e.r. 88:12*
2de: R^1 = Br	62% - *e.r. 88:12*	76% - *e.r. 87:13*
2ee: R^1 = N_3	76% - *e.r. 89:11*	90% - *e.r. 89:11*
2fe: R^1 = *t*-Bu	85% - *e.r. 92:8*	92% - *e.r. 91:9*
2ge: R^1 = *i*-Pr	85% - *e.r. 91:9*	72% - *e.r. 90:10*
2he: R^1 = Me	80% - *e.r. 92:8*	
2ie: R^1 = CF_3	40% - *e.r. 90:10*	
2je: R^1 = TMS—≡—CH_2	57% - *e.r. 88:12*	57% - *e.r. 88:12*
2ke: R^1 = Ph	84% - *e.r. 90.5:9.5*	90% - *e.r. 90:10*
2le: R^1 = *p*-$MeOC_6H_4$	83% - *e.r. 92:8*	97% - *e.r. 92:8*
2me: R^1 = *p*-MeC_6H_4	90% - *e.r. 94.5:5.5*	99% - *e.r. 90:10*
2ne: R^1 = *p*-*t*-BuC_6H_4	82% - *e.r. 92.5:7.5*	88% - *e.r. 91:9*
2oe: R^1 = OMe	81% - *e.r. 81.5:18.5*	80% - *e.r. 81:19*
2pe: R^1 = *p*-$MeOC_6H_4$	74% - *e.r. 81:19*	
2qe: R^1 = *p*-*t*-BuC_6H_4	76% - *e.r. 85:15*	
2re	40% - *e.r. 81:19*	
2se	56% - *e.r. 83:17*	
2te	62% - *e.r. 87:13*	

Scheme 2. Scope of the asymmetric benzylic C(sp^3)—H amination reaction.

The C(sp^3)—H amination was found to tolerate both electron-withdrawing (**2ce**, **2de**, **2ie**) and electron-donating (**2be**, **2he**, **2k-ne**) substituents. However, higher conversions are observed with electron-rich substrates that better react with the electrophilic rhodium-bound nitrene. Increasing the bulkiness of the substituents proved beneficial as the highest e.r. were obtained in the presence of a *t*-butyl or an aryl group (compounds **2fe**, **2k-ne**). Also worth of mention is the complete regioselectivity in favor of the ethyl substituent observed in the case of compounds **2ge** and **2je** for which two benzylic positions are available. Substrates with longer side chains were also investigated and the corresponding compounds **2o-re** could be isolated again with good yields in the 40-81% range though the e.r. were found to erode. A similar observation was made with the *meta*-substituted product **2se** and the dibenzosuberone derivative **2te**.[28]

The reaction conditions involving 1 mol% of Rh_2(*S*-tfptad)$_4$ **4b** were then applied to more complex substrates (Figure 2). Thus, starting from a protected analog of methyl dehydroabietate, a single isomer **2ue** was isolated in 65% yield.[29] On the other hand, excellent chemoselectivity was observed with the derivatives of sulbactam **2ve**, and cinnamic acid **2we** as the reaction only proceeds at the benzylic ethyl moiety.

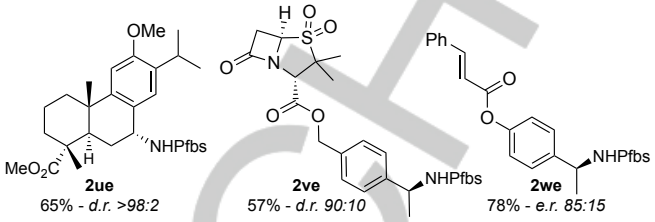
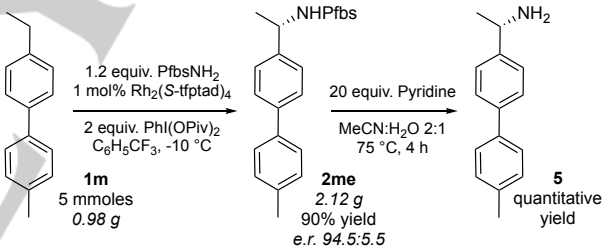


Figure 2. Chemo- and stereoselective late-stage C(sp^3)—H amination.

Finally, the C(sp^3)—H amination reaction can be performed on a gram-scale with equal efficiency. Starting from 5 mmoles of **1m**, the corresponding product **2me** was isolated in 90% yield and with an e.r. of 94.5:5.5 (Scheme 3). Fundamentally, an X-ray structure of compound **2me** led us to conclude that the use of the Rh_2(*S*-tfptad)$_4$ complex induces the formation of the (*S*)-enantiomer (see supporting information). We, then, demonstrated the ability to cleave the sulfamoyl group under mild conditions. Treatment of **2me** with pyridine in a 2:1 mixture of acetonitrile and water at 75 °C affords the free amine **5** in quantitative yield.



Scheme 3. Gram-scale reaction and removal of the Pfbs protecting group.

In conclusion, the combination of the pentafluorobenzyl sulfamate $PfbsNH_2$ **3e** with the chiral rhodium complex Rh_2(*S*-tfptad)$_4$ **4b** has led to the development of a catalytic asymmetric intermolecular C(sp^3)—H amination reaction with a wide scope. Excellent yields of up to 99% and ees of up to 89% have been obtained from substrates used in stoichiometric amounts, a result that underscores the high reactivity of benzylic sulfamates as nitrene sources. The reaction can be performed on a mmole scale with equal efficiency and the corresponding products can be easily deprotected under mild conditions without epimerization.

Worth of mention is the low loading (0.1 to 1 mol%) of the chiral rhodium catalyst **4b**. The excellent yields obtained for the products **2** demonstrate the very high catalytic activity of Rh_2(*S*-tfptad)$_4$ that proves stable under the oxidizing conditions.[30] While the catalyst loading remains higher than that reported by Arnold with mutated enzymes, both enantiomers of the rhodium complex **4b** are accessible thereby offering the opportunity to prepare both enantiomers of benzylic amines. Work is in progress to further investigate the new catalytic system in order to depict a

stereochemical model and develop a general method for catalytic asymmetric intermolecular C(sp^3)—H amination.

Acknowledgements

We wish to thank the French National Research Agency (program n° ANR-11-IDEX-0003-02, CHARMMMAT ANR-11-LABX-0039, and ANR-15-CE29-0014-01; fellowship to A. N.), the Ministère de l'Enseignement Supérieur et de la Recherche (fellowship to V. B.), and the ECOS-Sud Committee (Action A15E04), for their support. We are grateful to Marie Sircoglou (ICMMO, Université Paris-Sud) for helpful discussions.

Keywords: amination • enantioselective • rhodium • C—H functionalization • nitrene

[1] a) R. Hili, A. K. Yudin, *Nature Chem. Biol.* **2006**, *6*, 284; b) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257.

[2] F. W. Goldberg, J. G. Kettle, T. Kogej, M. W. D. Perry, N. P. Tomkinson, *Drug Discov. Today* **2015**, *20*, 11.

[3] T. C. Nugent, Ed.; *Chiral Amine Synthesis*, Wiley-VCH, Weinheim, **2010**.

[4] a) C. G. Newton, S.-G. Wang, C. C. Oliveira, N. Cramer, *Chem. Rev.* **2017**, *117*, 8908; b) T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu, J.-Q. Yu, *Science* **2018**, *359*, eaao4798.

[5] For reviews on C–H amination, see: a) F. Collet, R. H. Dodd, P. Dauban, *Chem. Commun.* **2009**, 5061; b) D. N. Zalatan, J. Du Bois, *Top. Curr. Chem.* **2010**, *292*, 347; c) J. L. Jeffrey, R. Sarpong, *Chem. Sci.* **2013**, *4*, 4092; d) M.-L. Louillat, F. W. Patureau, *Chem. Soc. Rev.* **2014**, *43*, 901; e) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247.

[6] For reviews on C–H amination with nitrenes, see: a) P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905; b) M. M. Díaz-Requejo, P. J. Pérez, *Chem. Rev.* **2008**, *108*, 3379; c) J. W. W. Chang, T. M. U. Ton, P. W. H. Chan, *Chem. Rec.* **2011**, *11*, 331; d) J. L. Roizen, M. E. Harvey, J. Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911; e) T. Uchida, T. Katsuki, *Chem. Rec.* **2014**, *14*, 117; f) D. Intrieri, P. Zardi, A. Caselli, E. Gallo, *Chem. Commun.* **2014**, *50*, 11440; g) J. Buendia, G. Grelier, P. Dauban, *Adv. Organomet. Chem.* **2015**, *64*, 77; h) J. M. Alderson, J. R. Corbin, J. M. Schomaker, *Acc. Chem. Res.* **2017**, *50*, 2147; i) D. Hazelard, P.-A. Nocquet, P. Compain, *Org. Chem. Front.* **2017**, *4*, 2500; j) B. Darses, R. Rodrigues, L. Neuville, M. Mazurais, P. Dauban, *Chem. Commun.* **2017**, ***53***, 493.

[7] For reviews, see: a) F. Collet, C. Lescot, P. Dauban, *Chem. Soc. Rev.* **2011**, *40*, 1926; b) W.-T. Wu, Z.-P. Yang, S.-L. You, in *Asymmetric Functionalization of C—H Bonds* (Ed.: S.-L. You), RSC Catalysis Series, **2015**, N° 25, pp. 1-66. For asymmetric amination by C—H activation, see: S. Fukagawa, Y. Kato, R. Tanaka, M. Kojima, T. Yoshino, S. Matsunaga, *Angew. Chem. Int. Ed.* **2019**, *58*, 1153; *Angew. Chem.* **2019**, *131*, 1165.

[8] a) J.-L. Liang, S.-X. Yuan, J.-S. Huang, W.-Y. Yu, C.-M. Che, *Angew. Chem. Int. Ed.* **2002**, *41*, 3465; *Angew. Chem.* **2002**, *114*, 3615; b) D. N. Zalatan, J. Du Bois *J. Am. Chem. Soc.* **2008**, *130*, 9220; c) E. Milczek, N. Boudet, S. Blakey *Angew. Chem., Int. Ed.* **2008,** *47*, 6825; *Angew. Chem.* **2008**, *120*, 6931.

[9] a) M. Ichinose, H. Suematsu, Y. Yasutomi, Y. Nishioka, T. Ichida, T. Katsuki *Angew. Chem. Int. Ed.* **2011**, *50*, 9884; *Angew. Chem.* **2011**, *123*, 10058; b) J. A. McIntosh, P. S. Coelho, C. C. Farwell, Z. J. Wang, J. C. Lewis, T. R. Brown, F. H. Arnold, *Angew. Chem. Int. Ed.* **2013**, *52*, 9309; *Angew. Chem.* **2013**, *125*, 9479; c) R. Singh, M. Bordeaux, R. Fasan, *ACS Catal.* **2014**, *4*, 546; d) P. Dydio, H. M. Key, H. Hayashi, D. S. Clark, J. F. Hartwig, *J. Am. Chem. Soc.* **2017**, *139*, 1750; e) C. Li, K. Lang, H. Lu, Y. Hu, X. Cui, L. Wojtas, X. P. Zhang, *Angew. Chem. Int. Ed.* **2018**, *57*, 16837; *Angew. Chem.* **2018**, *130*, 17079; f) Z. Zhou, S. Chen, J. Qin, X. Nie, X. Zheng, K. Harms, R. Riedel, K. N. Houk, E. Meggers, *Angew. Chem. Int. Ed.* **2019**, *58*, 1088; *Angew. Chem.* **2019**, *131*, 1100.

[10] I. Nägeli, C. Baud, G. Bernardinelli, Y. Jacquier, M. Moran, P. Müller, *Helv. Chim. Acta* **1997**, *80*, 1087.

[11] M. Yamawaki, H. Tsutsui, S. Kitagaki, M. Anada, S. Hashimoto, *Tetrahedron Lett.* **2002**, *43*, 9561.

[12] R. P. Reddy, H. M. L. Davies, *Org. Lett.* **2006**, *8*, 5013.

[13] The same results were by Katsuki with a tetrabromosalen complex. See: Y. Kohmura, T. Katsuki *Tetrahedron Lett.* **2001**, *42*, 3339.

[14] C. G. Espino, K. W. Fiori, M. Kim, J. Du Bois, *J. Am. Chem. Soc.* **2004**, *126*, 15378.

[15] T. Höke, E. Herdtweck, T. Bach, *Chem. Commun.* **2013**, *49*, 8009.

[16] Y. Nishioka, T. Uchida, T. Katsuki, *Angew. Chem. Int. Ed.* **2013**, *52*, 1739; *Angew. Chem.* **2013**, *125*, 1783.

[17] C. K. Prier, R. K. Zhang, A. R. Buller, S. Brinkmann-Chen, F. H. Arnold, *Nat. Chem.* **2017**, *9*, 629.

[18] K. Guthikonda, J. Du Bois, *J. Am. Chem. Soc.* **2002**, *124*, 13672.

[19] M. Okada, S. Iwashita, N. Koizumi, *Tetrahedron Lett.* **2000**, *41*, 7047.

[20] 2,6-difluorobenzyl sulfamate **3d** gives lower yields at -10 °C.

[21] a) K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2007**, *129*, 562; b) E. N. Bess, R. J. DeLuca, D. J. Tindall, M. S. Oderinde, J. L. Roizen, J. Du Bois, M. S. Sigman, *J. Am. Chem. Soc.* **2014**, *136*, 5783; c) N. D. Chiappini, J. B. C. Mack, J. Du Bois, *Angew. Chem. Int. Ed.* **2018**, *57*, 4956; *Angew. Chem.* **2018**, *130*, 5050.

[22] The improved enantioselectivity could be rationalized by halogen-binding interactions that contribute to rigidify the chiral crown conformation of the paddlewheel complex. See: V. N. G. Lindsay, W. Lin, A. B. Charette, *J. Am. Chem. Soc.* **2009**, *131*, 16383.

[23] The (*S*)-tfptad ligand and its 3,5-dimethyl analogue were prepared in 5 steps from the corresponding 1-adamantanemethanol, respectively in 47% and 6% yield. See the supporting information for the preparation of the (*S*)-tfptad ligand and the X-ray structure of the Rh_2(*S*-tfptad)$_4$ complex.

[24] Lower yields were observed for reactions performed at -20 °C.

[25] Various additives have been screened to improve the yield and enantioselectivity, however, unsuccessfully (see table S2 in the Supporting Information). For a review on the effect of additives, see: A. F. Trindade, J. A. S. Coelho, C. A. M. Afonso, L. F. Veiros, P. M. P. Gois, *ACS Catal.* **2012**, *2*, 370.

[26] The increased in enantioselectivity with a lower catalyst loading has already been observed with bifunctional organocatalysts. See: a) G. Rulli, N. Duangdee, K. Baer, W. Hummel, A. Berkessel, H. Gröger, *Angew. Chem. Int. Ed.* **2011**, *50*, 7944; *Angew. Chem.* **2011**, *123*, 8092; b) H. B. Jang, H. S. Rho, J. S. Oh, E. H. Nam, S. E. Park, H. Y. Bae, C. E. Song, *Org. Biomol. Chem.* **2010**, *8*, 3918.

[27] The e.r. can be enriched by recrystallization as, for example, in the case of **2ne** that could be obtained with an e.r. of 96:4.

[28] Similar lower yields with alkylarenes or *meta*-substituted arenes were observed in our studies with sulfonimidamides. These were attributed to steric effects. See: a) F. Collet, C. Lescot, C. Liang, P. Dauban, *Dalton Trans.* **2010**, *39*, 10401; b) J. Buendia, B. Darses, P. Dauban, *Angew. Chem.* **2015**, *127*, 5789; *Angew. Chem. Int. Ed.* **2015**, *54*, 5697.

[29] The reaction between the same abietane analog with $TcesNH_2$ in the presence of 2 mol% of Rh_2(esp)$_2$ led to the formation of the Tces-substituted product in 70% yield and with a d.r. of 5:1.

[30] A previous study revealed that chiral dirhodium tetracarboxylates derived from α-amino acids cannot provide good enantiocontrol in the presence of [bis(acyloxy)iodo]arenes because of ligand exchanges. See ref. 8b

10.1002/anie.201902882

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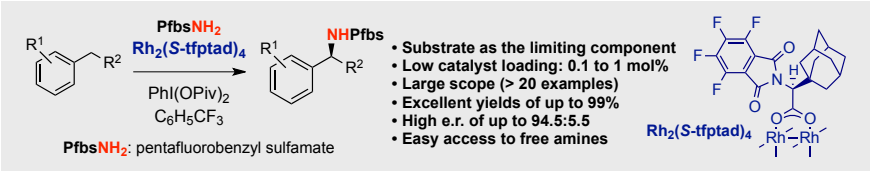

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Catalytic Enantioselective Intermolecular Benzylic C(sp^3)—H Amination

Benz to benz. A practical method for asymmetric intermolecular benzylic C(sp^3)—H amination is reported. The latter is based on the combination of the pentafluorobenzyl sulfamate PfbsNH$_2$ with the chiral rhodium(II) catalyst Rh$_2$(*S*-tfptad)$_4$. Various substrates, used as limiting components, are converted to benzylic amines with excellent yields and high levels of enantioselectivity. The Pfbs group can be removed under mild conditions to afford the NH-free benzylic amines.