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Stereoselective intermolecular C–H amination reactions†

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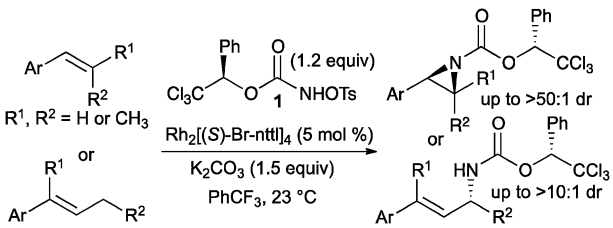
A novel chiral *N*-mesyloxycarbamate to perform rhodium-catalyzed stereoselective C–H amination reactions is reported. Chiral benzylic and propargylic amines are produced in good yields and selectivities using ethyl acetate as solvent. The corresponding free amines are easily obtained by cleavage of the chiral reagent, which could also be recovered.

Catalytic C–H insertion reactions are green alternatives to traditional synthetic methods using pre-functionalized substrates.[1] Recently, novel stereoselective C–H bond oxidation reactions to produce alcohols have been successfully developed to streamline the synthesis of complex organic molecules.[2] In comparison, methods to introduce nitrogen into C–H bonds are still in their infancy, particularly in the stereoselective manifold.[3] Metal nitrenes typically produced from azides[4] or iminoiodinanes,[5] are intermediates known to react with electron-rich C–H bonds.[3,6] Whereas a number of intramolecular C–H aminations have been reported,[7] only a few intermolecular processes have been described.[7c,d,8] However, given the biological significance of the products resulting from this transformation (chiral amines), novel amination reactions of C–H bonds are highly desirable.

The development of chiral catalysts to achieve intermolecular enantioselective C–H amination proved to be challenging; chiral metal catalysts derived from Rh(II),[7d,8a,d,g] Ru(II)[8c] and Mn(II)[8b,c] complexes have so far been reported. High enantioselectivities could be achieved using chiral Rh(II) catalysts, although only with a very limited number of substrates.[8g] The state-of-the-art in stereoselective C–H amination reactions has been reported by Muller, Dodd, Dauban and co-workers,[8f,i] who exploited the concept of double stereodifferenciation. In the presence of a chiral rhodium dimer catalyst, the amination of alkanes with a chiral sulfonimidamide and $PhI(O_2C\textit{t}\text{-}Bu)_2$, produced protected benzylic and allylic amines with high yields and levels of stereoinduction. However, a few drawbacks are still associated with this process[9] and the development of more practical and ecofriendly reaction conditions is highly desirable.

Our group has introduced *N*-tosyloxycarbamates as alternative precursors to produce metal nitrenes from rhodium dimer and copper catalysts, that undergo C–H amination and aziridination reactions with high efficiency.[10] Using these reagents, no extra oxidant is required and the by-product is potassium tosylate (MW = 210), which is easily removed by a simple filtration. We have recently shown that when using chiral *N*-tosyloxycarbamate **1** and Rh_2[(*S*)-Br-nttl]$_4$, good yields and diastereoselectivities were obtained for intermolecular aziridination and allylic C–H amination of aromatic alkenes (Scheme 1).[11] The amination reaction proceeded at rt in only 90 min in chlorinated or benzene derived solvents. Consequently, searching for an alternative, green and biodegradable solvent was identified as an important goal for future work. Chiral reagent **1** is readily prepared from (*R*)-1-phenyl-2,2,2-trichloroethanol, which is available in large quantities *via* catalytic asymmetric reduction; the chiral alcohol can also be recovered after cleavage. Decreasing the molecular weight of the chiral reagent, while generating only biodegradable by-product were also identified as goals which would significantly improve the environmental impact of the process.



Scheme 1 Stereoselective amination of alkenes with chiral reagent **1**.[11]

Herein, we report the amination of *benzylic* and *propargylic* C–H bonds with chiral *N*-mesyloxycarbamate **2** in ethyl acetate that leads to the desired products in good yields and selectivities while generating biodegradable by-products.

Benzylic C–H bonds are known to be reactive toward metal nitrene species. The amination of ethylbenzene was thus investigated with reagent **1**.[12] We found that solvents such as isopropyl and ethyl acetate,[13] were compatible with the reaction conditions. Furthermore, the *p*-toluenesulfonyl leaving group could be replaced by methanesulfonyl.[14] With *N*-mesyloxycarbamate **2** the molecular weight of the chiral reagent is decreased and the resulting by-product is now potassium methanesulfonate, which after protonation produced methanesulfonic acid, known to be biodegradable.[15] Green reaction conditions, that involved 1 equiv of the alkane, 1.2 equiv of **2** using 2 mol% of rhodium catalyst and 3 equiv of potassium acetate in ethyl acetate, produced chiral amine **3** in 58% yield and 54 : 1 dr (Table 1, entry 1). Other diversely

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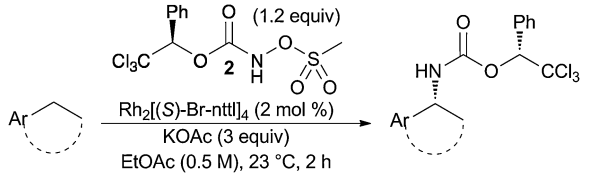
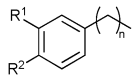
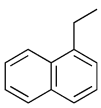
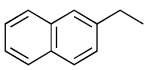
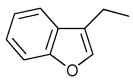
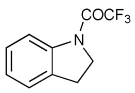
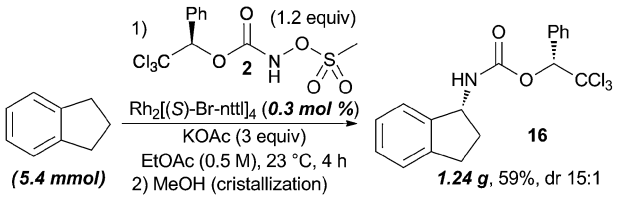
Table 1 Stereoselective rhodium-catalyzed benzylic C–H amination with chiral *N*-mesyloxycarbamate **2**



Entry[a]	Alkane	Crude dr[b]	Yield[c], dr[d]
			
	$n = 1$		
1	$R^1 = R^2 = H$	7.8 : 1	(**3**) 58%, 54 : 1
2	$R^1 = H$, $R^2 = t$-Bu	12 : 1	(**4**) 70%, >99 : 1
3	$R^1 = H$, $R^2 = MeO$	11 : 1	(**5**) 64%, 18 : 1
4	$R^1 = H$, $R^2 = Br$	9.1 : 1	(**6**) 74%, >99 : 1
5	$R^1 = H$, $R^2 = AcO$	10 : 1	(**7**) 80%, 11 : 1
6	$R^1 = R^2 = MeO$	18 : 1	(**8**) 82%, 43 : 1
	$n = 2$		
7	$R^1 = H$, $R^2 = Br$	5.1 : 1[e]	(**9**) 63%, >99 : 1[e]
8	$R^1 = H$, $R^2 = Ac$	6.6 : 1[e]	(**10**) 68%, 7.4 : 1[e]
9	$R^1 = H$, $R^2 = OAc$	10 : 1	(**11**) 58%, 12 : 1
10	$R^1 = R^2 = MeO$	8.0 : 1	(**12**) 59%, 8.5 : 1
11		39 : 1	(**13**) 73%, 95 : 1
12		15 : 1	(**14**) 73%, >99 : 1
13		17 : 1	(**15**) 62%, 47 : 1
14		13 : 1	(**16**) 70%, 14 : 1
15		7.0 : 1	(**17**) 80%, 14 : 1
16		28 : 1	(**18**) 93%, 46 : 1
17		7.0 : 1	(**19**) 75%, 52 : 1

[a] Reactions were conducted on 0.25 mmol of alkane. [b] *R*,*R* : *S*,*R* ratio as determined by HPLC on the crude material. [c] Isolated yield. [d] *R*,*R* : *S*,*R* ratio as determined by HPLC on the purified material. [e] *R*,*R* : *S*,*R* ratio as determined by SFC analysis.

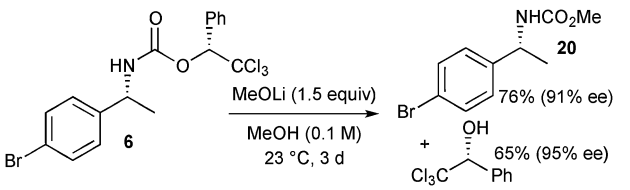
substituted benzylic amines were produced with crude diastereomeric ratios around 10 : 1 (entries 2–6). These drs could be easily enhanced by a simple flash chromatography or recrystallization, thus chiral amines with >99 : 1 dr were isolated (entries 2 and 4). The stereoselective C–H amination was not limited to ethylbenzene derivatives. The reaction of *n*-propylbenzene substrates also favoured insertion at the benzylic position and the corresponding protected amines were isolated in 58–68% yield (entries 7–10). The crude diastereomeric ratios



Scheme 2 Gram-scale stereoselective C–H amination of indane.

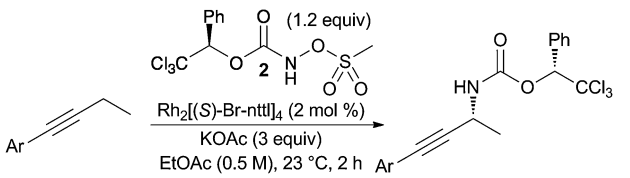
varied from 5 : 1 to 10 : 1 and it was again possible to enhance the ratio *via* chromatography to isolate a single diastereomer (product **9**, entry 7). Excellent diastereoselectivities were observed with naphthyl derivatives (entries 11–12). Amine **13** was easily purified by recrystallization to afford a single diastereomer: an X-ray crystal structure was obtained to confirm the absolute stereochemistry. The C–H amination reaction was also compatible with heteroaromatic substrates and the protected amine derived from 2-ethylbenzofurane was isolated in 62% yield with 47 : 1 dr (entry 13).[16] Cyclic substrates also provided good results. For example, the amination of indane proceeded in good yields and dr using **2** (entry 14). The reaction was easily scalable; on 5.4 mmol scale using 0.3 mol% of $Rh_2[(S)\text{-Br-nttl}]_4$, 1.24 g (59%; 15 : 1 dr) of protected amine **16** was isolated after purification by recrystallization (Scheme 2).

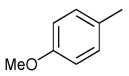
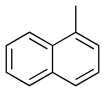
The reaction conditions were compatible with a ketone group as product **17** was obtained in excellent yield (entry 15, see also entry 8). The benzylic C–H amination was favoured over insertion into C–H bond α to oxygen as shown with dihydrobenzofuran (entry 16). The regioselective benzylic C–H amination of dihydroindole also proceeded in good yield when the nitrogen was protected as a trifluoroacetamide (entry 17).



Scheme 3 Methanolysis of chiral carbamate **6**.

Table 2 Stereoselective and regioselective rhodium-catalyzed propargylic C–H amination reactions

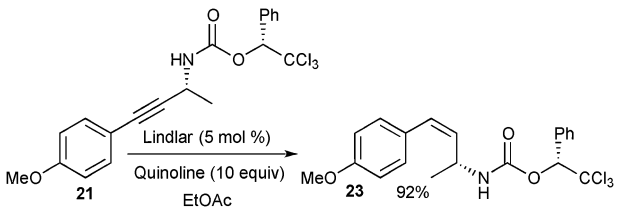


Entry[a]	Ar	Crude dr[b]	Yield[c], dr[d]
1		27 : 1	(**21**) 50%, >99 : 1
2		7.0 : 1	(**22**) 62%, 52 : 1

[a] Reactions were conducted on 0.25 mmol of alkane. [b] *R*,*R* : *S*,*R* ratio as determined by HPLC on the crude material. [c] Isolated yield. [d] *R*,*R* : *S*,*R* ratio as determined by HPLC on the purified material.

One advantage of the current technology is the facile cleavage and recovery of the chiral alcohol. For instance, methanolysis of amine **6** produced methylcarbamate **20** in good yields and high enantiomeric excess (Scheme 3).[17] (*R*)-1-Phenyl-2,2,2-trichloroethanol was also recovered in good yields and enantiomeric excess, thus making the chiral reagent recyclable.

To further extend the substrate scope, the propargylic amination of alkynes was studied (Table 2). We were pleased to find that propargylic amine **21** was produced with 27 : 1 crude dr (entry 1). The desired product was isolated as a single diastereomer in 50% yield. Similarly, amine **22** was isolated in 62% and 52 : 1 dr (entry 2). To the best of our knowledge, this is the first example of a metal nitrene propargylic intermolecular C–H amination reaction.[18] It was possible to reduce the alkyne to the *Z*-allylic amine **23** in 92% yield (Scheme 4).



Scheme 4 Hydrogenation of chiral carbamate **21**.

In conclusion, readily available chiral *N*-mesyloxycarbamate **2** was used to perform stereoselective C–H amination reactions. The scope of the process was extended to produce benzylic and propargylic amines in good yields and dr. The reaction was performed in ethyl acetate and produced biodegradable by-products. After cleavage, both chiral amine and the chiral alcohol derived from reagent **2** were recovered in high yields and ee.

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9 Reaction run at −35 °C for 3 d under Ar in anhydrous TCE/MeOH; not recoverable chiral auxiliary used; $PhI(O_2Ct\text{-}Bu)_2$ (MW = 406) used to generate the corresponding iminoiodinane.

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12 See ESI for details†.

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14 TGA showed that reagent **2** is stable up to 180 °C. An X-ray crystal structure **2** was obtained. See ESI for details†.

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16 No aziridination product was observed.

17 It was also possible to hydrolyze the chiral carbamate using zinc in acetic acid to produce the corresponding amine with no loss of enantiomeric excess; see ESI for details†.

18 For a recent example of intramolecular nitrene propargylic C–H amination reaction, see: R. D. Grigg, J. W. Rigoli, S. D. Pearce and J. M. Schomaker, *Org. Lett.*, 2012, **14**, 280.