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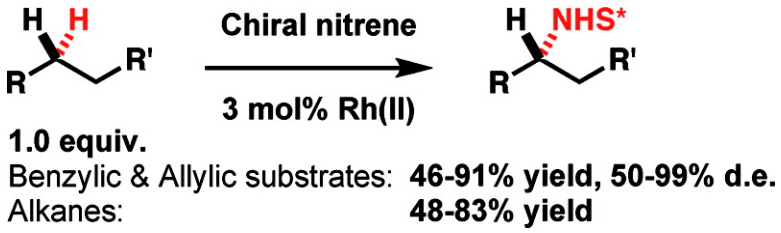

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Toward a Synthetically Useful Stereoselective C−H Amination of Hydrocarbons

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Abstract: Reaction between a sulfur(VI) compound and an iodine(III) oxidant in the presence of a catalytic quantity (≤3 mol %) of a rhodium(II) catalyst leads to the formation of a chiral metallanitrene of unprecedented reactivity. The latter allows intermolecular C−H amination to proceed in very high yields up to 92% and excellent diastereoselectivities up to 99% with C−H bond containing starting materials as the limiting component. The scope of this C−H functionalization includes benzylic and allylic substrates as well as alkanes. Secondary positions react preferentially, but insertion into activated primary C−H bonds or sterically accessible tertiary sites is also possible. Cooperative effects between the nitrene precursor and the chiral catalyst at the origin of these good results have also been applied to kinetic resolution of racemic sulfonimidamide. This methodology paves the way to the use of Csp^3−H bonds as synthetic precursors for the introduction of a nitrogen functionality into selected positions.

Introduction

The amino function plays a pivotal role in both chemistry and biology. Nitrogen is thus found in some of the major natural product classes such as amino acids or alkaloids as well as in a wealth of pharmaceutical agents where its presence strongly influences both their pharmacodynamic properties and their bioavailability.[1] The key importance of nitrogen has therefore inspired chemists over the years to design a wide array of methodologies for C−N bond formation.[2] The advent of transition metal complexes has led to the development of efficient catalytic procedures such as hydroamination of olefins[3] or the Buchwald−Hartwig C−N couplings,[4] to name but a few. The majority of these, however, requires the incorporation of a functionality prior to the introduction of the nitrogen atom.

With the aim of discovering new efficient synthetic strategies for the preparation of amino compounds, the direct transformation of a C−H into a C−N bond appears highly appealing especially if the selective functionalization of a unique C−H bond can be achieved. In parallel to the development of efficient synthetic strategies for the regioselective formation of C−C, C−O, C−B, or C−X bonds starting from C−H bonds,[5] the area of catalytic C−H amination has been recently intensively investigated and has led to significant results arising from the discovery of simple efficient nitrene transfers.[6] The latter species could be generated from azides,[7] haloamines,[8] or *N*-arenesulfonyloxycarbamates.[9,10] However, the most notable achievements have been made to date by using iminoiodanes,[11] hypervalent

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iodine(III) reagents of general formula PhI=NR which are now easily handled.[12] Rhodium(II) complexes have been found to be the catalysts of choice to perform amination of various C−H bonds[11b,12b,13] but ruthenium,[12a,14] manganese,[12a,14a,b,15] copper,[16] palladium,[17] and silver[18] based systems can also be used. Nevertheless, despite this plethora of nitrene precursors and transition metal catalysts, the efficiency of the subsequent C−H functionalization is almost always dependent upon the involvement of an internal tether. While intramolecular C−H amination is now a well-established methodology that has found applications in total synthesis,[19] the intermolecular version, by contrast, suffers from being low yielding[20] and limited in scope to benzylic positions and cyclic ethers. Moreover, the rare examples of enantioselective intermolecular nitrene C−H insertions reported so far involve substrates used in excess. This work therefore reports our recent efforts aimed at developing a *catalytic stereoselective intermolecular C−H amination of various types of hydrocarbons used in stoichiometric amounts*. The high reactivity of the system based on cooperative effects between a chiral rhodium(II) complex **1** and a sulfonimidamide **2** is one of the key elements allowing the efficient selective C−H functionalization of benzylic and allylic substrates as well as simple alkanes.

Results and Discussion

Initial Results. Sulfonimidamides are analogues of sulfonamides in which one of the oxygen atoms of the sulfonyl moiety has been replaced by a nitrogen group thereby making these sulfur(VI) compounds chiral. They were first described by Levchenko in the early 1960s[21] but rarely used since then in organic synthesis.[22] Recent development of simple methodologies for the *in situ* generation of iminoiodanes[12] from various nitrogen sources (i.e., sulfonamides, sulfamates, or carbamates) prompted us to apply these conditions to sulfonimidamides. We were thus very pleased to observe that, in our hands, these reagents appear to be highly useful for the generation of chiral nitrenes and their subsequent catalytic transfer. While their use in the copper-catalyzed aziridination of olefins met with limited success,[23] the combination of the enantiomerically pure sulfonimidamide (*S*)-**2a** with the chiral rhodium(II) complex [Rh_2-{(*S*)-nttl}$_4$] **1a** as catalyst allowed us to discover a highly efficient diastereoselective intermolecular C−H amination with the C−H bond-containing substrate being the limiting component (Figure 1).[24]

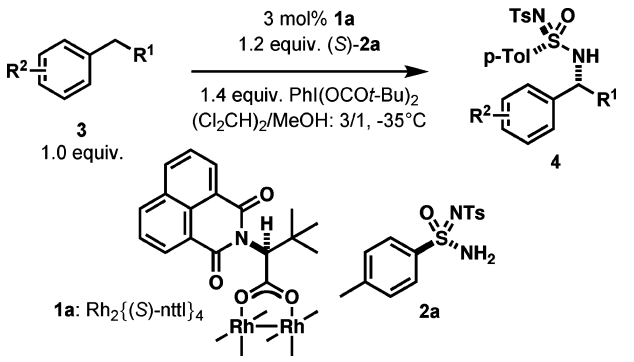

Figure 1. Diastereoselective rhodium-catalyzed benzylic C−H amination using sulfonimidamide **2a**.

This efficient transformation is the consequence of an initial screening of various reaction parameters using tetrahydronaphthalene **3a** as a test substrate (see Supporting Information). We thus found suitable conditions that involve use of 1.4 equiv of the commercially available bis(*tert*-butylcarbonyloxy)iodosylbenzene PhI(OCO*t*-Bu)$_2$ in a 3:1 mixture of 1,1,2,2-tetrachloroethane/MeOH at −35 °C.[24] Dichloromethane can also be used instead of $(Cl_2CH)_2$, but yields are lower. The combination of a halogenated solvent with methanol provides a completely homogeneous reaction medium. Methanol allows solubilization of the sulfonimidamide, but its compatibility with the catalytic nitrene transfer is clearly unexpected (*vide infra*). As far as the oxidizing reagent is concerned, use of a slight excess of the soluble PhI(OCO*t*-Bu)$_2$ was shown to give higher yields than those observed with the more commonly used PhI(OAc)$_2$ and PhI=O. Increasing the amount of PhI(OCO*t*-Bu)$_2$ up to 2 equiv does not improve the yields significantly (*vide infra*), while lengthening reaction times does.

Under these conditions, very good yields up to 93% but also excellent diastereoselectivities up to 99% could be obtained

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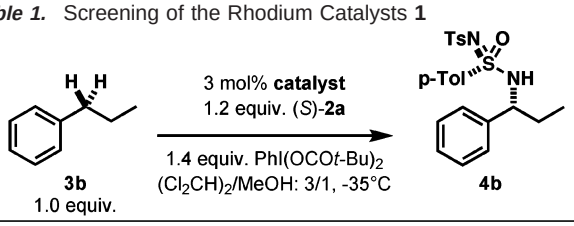
though only in the case of secondary benzylic positions. These unprecedented results both in terms of reactivity and selectivity then encouraged further investigations in order to develop an efficient catalytic C−H amination of broadened scope, particularly with respect to allylic derivatives and simple alkanes. Moreover, the strongly matched effect observed between the (*S*)- (or (*R*)-) sulfonimidamide and the (*S*)- (or (*R*)-) rhodium complex could be beneficial to the implementation of a simplified procedure involving the use of more readily prepared racemic sulfur(VI) reagents.

Optimization by Reagent Screening. In order to improve the efficiency of the nitrene transfer, we decided to focus successively on the structure of rhodium catalysts **1** and sulfonimidamides **2** as well as on the nature of the cosolvent. Propylbenzene **3b** was used as a test substrate since the above conditions afforded the corresponding C−H aminated product **4b** with a good diastereoselectivity of 90% but a low yield of 28%.

We first screened a variety of rhodium(II) complexes **1b**−**h** prepared, as was [Rh_2((*S*)-nttl)$_4$], from $Rh_2(OAc)_4$ by simple ligand exchange according to the previously published procedure involving Soxhlet extraction in refluxing chlorobenzene.[25] Various amino acids with different nitrogen protecting groups could therefore be installed on the dirhodium core. On one hand, modification of the side chain revealed that higher yields are obtained by decreasing the size of the substituent (Table 1, entries 1−4), the most active catalyst being the less sterically demanding complex [Rh_2{(*S*)-nta}$_4$] **1d** derived from alanine.[26] The C−H aminated product **4b** was then isolated with a better yield of 51% (entry 4). In all cases, a very good diastereoselectivity greater than 90% was obtained as indicated by ^{1}H NMR spectra. On the other hand, modification of the nitrogen protecting group (entry 5) or of its electron density (entries 6−8) led to lower yields compared to that obtained with catalyst **1d**. The latter was thus always used in the following experiments.

We then screened various substituted *N*-(*p*-toluenesulfonyl)-sulfonimidamides **2**.[27] These could be prepared from the corresponding sulfinyl chlorides[28] in two steps via the formation of sulfonimidoyl chlorides obtained by action of anhydrous chloramine-T.[29] Enantiopure reagents are also accessible by resolution using (*S*)- or (*R*)-α-methylbenzylamine.[22e] It thus appeared that the reactivity of the system was slightly improved by introduction of a nitro group or a chloro atom at the *para* position since the corresponding C−H aminated products **4bb** and **4bc** were isolated in 62% and 60% yields, respectively (Table 2, entries 2 and 3). The presence of the bulkier electron-withdrawing *p*-CF_3 or the electron-donating *p*-OMe, by contrast, did not improve the results (entries 4 and 5), while replacement of the aryl moiety by an ethyl chain led to the formation of the expected compound **4bf** in a very poor yield (entry 6).[30]

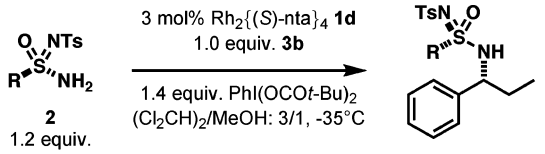
Table 1. Screening of the Rhodium Catalysts **1**



Entry	$Rh^{(II)}$ catalyst	Yield[a]	Entry	$Rh^{(II)}$ catalyst	Yield[a]
1	**1a**	28	5	**1e**	< 10
2	**1b**	31	6	**1f**	42
3	**1c**	43	7	**1g**	25
4	**1d**	51	8	**1h**	39

[a] Isolated yields.

Table 2. Screening of the Sulfonimidamides **2**



Entry	R (compd number)	Yield[a]
1	Me– **2a**	**4ba**: 51
2	O_2N– **2b**	**4bb**: 62
3	Cl– **2c**	**4bc**: 60
4	F_3C– **2d**	**4bd**: 43
5	MeO– **2e**	**4be**: 25
6	**2f**	**4bf**: < 10

[a] Isolated yields.

However, compared to sulfonimidamide **2a**, preparation of chloro analogue **2c** and, particularly, of nitro derivative **2b** starting from the corresponding thiols appeared to be tedious if enantiomerically pure reagents were needed (see Supporting Information). Since both reagents did not afford a significant

(25) Müller, P.; Allenbach, Y.; Robert, E. *Tetrahedron: Asymmetry* **2003**, *14*, 779−785.
(26) This result stands in contrast to previous studies devoted to rhodium-catalyzed carbene transfers where increase of the steric bulk led to more active catalysts. For example, see: Reddy, R. P.; Lee, G. H.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 3437−3440 and references therein.
(27) Initial studies have revealed that the *p*-toluenesulfonyl group on the imido function is optimal in terms of both reactivity and selectivity.
(28) Sulfinyl chlorides could be prepared by treatment of the corresponding sulfinate salts with thionyl chloride. When the sulfinate was not commercially available, it was prepared by oxidation of aromatic thiols with sulfuryl chloride and acetic acid. See: Youn, J.-H.; Herrmann, R. *Synthesis* **1987**, 72−73.
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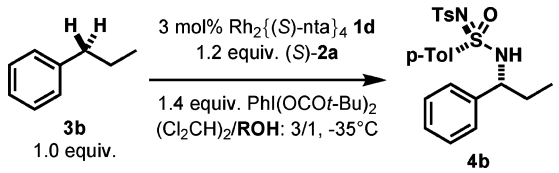
Table 3. Screening of the Protic Cosolvent



entry	ROH	yield[a]
1	MeOH	51
2	EtOH	12
3	*t*-BuOH	traces
4	*i*-PrOH	traces
5	$ClCH_2OH$	25
6	CF_3CH_2OH	20

[a] Isolated yields.

increase of reactivity (*vide infra*, ref 37), further investigations were carried out with compound **2a**.

A striking feature of the C−H amination involving sulfonimidamides is the need for methanol as a cosolvent in order to obtain good conversions.[31] This result was clearly unexpected since it is generally believed that protic solvents induce hydrolysis of iminoiodanes in the presence of transition metal complexes.[32] Several alcohols were screened in the context of the reaction between substrate **3b** and reagent **2a**. While higher homologues of methanol such as ethanol, isopropanol, or *tert*-butanol afforded only traces of the expected C−H aminated product (Table 3, entries 2−4), use of chloromethanol or trifluoroethanol allowed isolation of compound **4b** though with lower yields in the 20−25% range (entries 5 and 6).

At this time, we cannot propose an explanation for this exceptional effect. However, a possible role for methanol would be, in addition to the solubilization of the sulfonimidamide, its involvement in the formation of the iminoiodane. This process takes place *via* successive ligand dissociations and associations (*vide infra*) in which methanol could act as a ligand for the hypervalent iodine center.

Finally, the influence of the hypervalent iodine reagent on the results was again studied in the case of substrate **3b**. Use of $PhI(OAc)_2$ and PhIO once more led to lower yields of, respectively, 36% and 32%, while addition of 2.0 equiv of $PhI(OCOt\text{-}Bu)_2$ did not bring a significant improvement since the C−H aminated product **4b** was isolated in 56% yield (vs 51% yield with 1.4 equiv).

Scope of the Intermolecular C−H Amination. Using catalyst **1d** and sulfonimidamide **2a**, we investigated the scope of the intermolecular nitrene C−H insertion. Benzylic C−H amination was first studied, and the results obtained clearly demonstrate the higher catalytic activity of $[Rh_2\{(S)\text{-nta}\}_4]$ **1d** compared to **1a** (Table 4), while excellent diastereoselectivities generally greater than 97% were obtained. Use of only 0.5 mol % of **1d** thus affords the same results as those previously reported with 3 mol % of $[Rh_2\{(S)\text{-nttl}\}_4]$ **1a** in the case of substrates **3c** and **3d** (entries 3 and 4). Moreover, a substantial gain in yield up to 31% is observed with other secondary benzylic substrates (entries 2 and 5−7). It is also worth noting that the catalytic C−H amination proceeds efficiently in the presence of an electron-withdrawing group (entries 5 and 8). In the case of **3i** (entry 9), the reaction takes place regioselectively at the secondary benzylic position.[33] However, functionalization of a primary benzylic position was found to be possible starting from a stoichiometric amount of the substrate **3j** (entry 10). Examples of such C−H aminations are scarce, and all rely on the use of toluene and its derivatives as the solvent.[7a,16a]

We then turned our attention to nitrene C−H insertion into the more challenging allylic position. Allylamines are highly useful starting materials in organic synthesis, but their preparation is mainly based on nucleophilic allylic substitution, a process that requires initial functionalization of the substrate.[34,35] Very recently, the long-standing problem of allylic C−H amination was partly resolved with the discovery of a catalytic intramolecular procedure involving a π-allylpalladium intermediate.[36] However, a stereoselective intermolecular variant remained to be found. In this context, application of our procedure has now allowed us to develop such an allylic C−H functionalization in which the substrate is the limiting component. Very good yields up to 90% and diastereoselectivities up to 94% of the aminated products were thus obtained (Table 5).

An important feature of this process is that both cyclic and linear alkenes can be transformed with nearly equal efficiency using catalyst **1d** which once more is superior to **1a** in terms of reactivity and selectivity (entries 1 and 5).[37] The C−H aminated products **6** are obtained with complete regioselectivity, secondary allylic positions being more reactive than their primary counterparts (entries 2, 3, 6, and 7). Moreover, in the case of 1-substituted cyclic alkenes **5b**−**d** (entries 2−4), the regioselectivity is also governed by steric factors directing the C−H functionalization to the less hindered secondary allylic positions as confirmed by NOESY experiments and in agreement with results obtained by Davies in the field of rhodium-catalyzed carbene C−H insertion.[38] Finally, as previously observed, no competitive catalytic aziridination occurred contrary to what has been described using rhodium acetate[23b] or sulfonamides and sulfamates.[39] The difference in reactivity can be linked to the nature of the ligands bound to the rhodium catalyst. Such a

(30) Unexpectedly, starting from *N*-(*p*-toluenesulfonyl)-2,4,6-trimethylbenzenesulfonimidamide, only the product of intramolecular C−H amination at one of the *ortho*-methyl substituents was isolated. The scope of this reaction is under investigation.

(31) A test experiment allowed us to demonstrate that C−H amination could indeed occur in pure methanol. The expected product starting from 1.0 equiv of indane was thus isolated with a very good yield of 74% and an excellent de greater than 95%.

(32) (a) White, R. E. *Inorg. Chem.* **1987**, *26*, 3916−3919. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742−2753.

(33) Test experiments realized with tertiary benzylic substrates took place very sluggishly. As stated by Du Bois in ref 13g, the C−H amination is sensitive to steric effects.

(34) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689−1708.

(35) Noncatalytic direct allylic C−H aminations can be performed via ene-type reactions. For example, see: (a) Sharpless, K. B.; Hori, T. *J. Org. Chem.* **1976**, *41*, 176−177. (b) Sharpless, K. B.; Hori, T.; Truesdale, L. K.; Dietrich, C. O. *J. Am. Chem. Soc.* **1976**, *98*, 269−271. (c) Deleris, G.; Dunogues, J.; Gadras, A. *Tetrahedron* **1988**, *44*, 4243−4258.

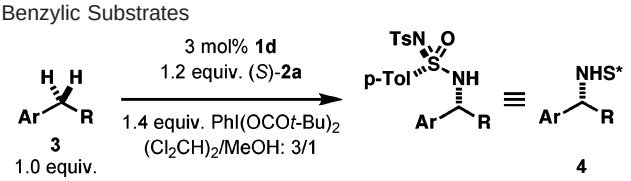
(36) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274−7276.

(37) In parallel reactions, the chlorosulfonimidamide **2c** was found to afford the corresponding C−H aminated products with similar yields and selectivities when compared to those obtained with **2a**. For example, the chloro analogues of compounds **6g** and **6h** were isolated in 82% and 73% yields, respectively, and with the same de of 89%.

(38) Davies, H. M. L.; Ren, P.; Jin, Q. *Org. Lett.* **2001**, *3*, 3587−3590.

(39) (a) Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672−13673. (b) Müller, P.; Baud, C.; Jacquier, Y.; Moran, M.; Nägeli, I. *J. Phys. Org. Chem.* **1996**, *9*, 341−347.

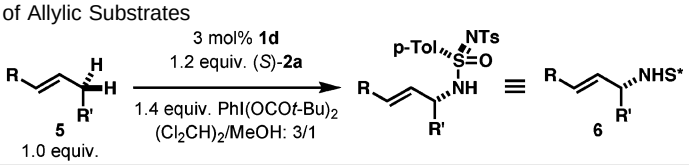
Table 4. Catalytic C−H Amination of Benzylic Substrates



Entry	Substrate	Product	Yield[a,b]	de[b,c]	Entry	Substrate	Product	Yield[a,b]	de[b,c]
1	3a	4a	86 (80)	98 (96)	6	3f	4f	91 (62)	99 (99)
2	3b	4b	51 (28)	95 (90)	7	3g	4g	91 (62)	98 (99)
3	3c	4c	89[d] (88)	98 (99)	8	3h	4h	82	97
4	3d	4d	92[d] (93)	98 (98)	9	3i	4i	81	98
5	3e	4e	82 (51)	87 (80)	10	3j	4j	46 (85)[e]	

[a] Isolated yields. [b] Values in parentheses were obtained with catalyst **1a**. [c] The de values were determined by HPLC (Hypercarb or Symmetry Shield Column). [d] 0.5 mol % of chiral catalyst **1d** was used. [e] Yield in parentheses obtained with catalyst **1d** using 5.0 equiv of **3j**.

Table 5. Catalytic C−H Amination of Allylic Substrates



Entry	Substrate	Product	Yield[a,b]	de[b,c]	Entry	Substrate	Product	Yield[a,b]	de[b,c]
1	5a	6a	86 (75)	50 (50)	5	5e	6e	85 (55)	69 (50)
2	5b	6b	75	90	6	5f	6f	66	60
3	5c	6c	90	90	7	5g	6g	82	87
4	5d	6d	85	94	8	5h	6h	79	89

[a] Isolated yields. [b] Values in parentheses were obtained with catalyst **1a**. [c] The de values were determined by HPLC (Hypercarb or Symmetry Shield Column).

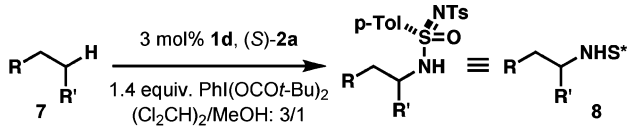
ligand effect on the chemoselectivity has already been reported in the field of carbene chemistry.[40]

The next step of our investigation was the application of our methodology to simple alkanes. C−H functionalization of the latter remains challenging since all previous studies have involved the use of a large excess of substrate in order to obtain good yields. We were thus very pleased to observe that, starting from a stoichiometric amount of cycloalkanes **7a**−**e** and only 3 mol % of rhodium catalyst **1d**, the corresponding C−H aminated products **8a**−**e** were isolated with yields in the 48−83% range while use of a 5-fold excess of substrate led to very good yields up to 96% (Table 6, entries 1−5).

These results compare favorably with the recently published silver-catalyzed process where yields of around 40% were

(40) For some examples, see: (a) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669−8680. (b) Doyle, M. P.; Phillips, I. M. *Tetrahedron Lett.* **2001**, *42*, 3155−3158. For a review, see: Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed.* **1994**, *33*, 1797−1815.

Table 6. Catalytic C−H Amination of Alkanes



Entry	Substrate	Product	Yield[a]	Yield[b]
1	7a	8a	48	85
2	7b	8b	50	85
3	7c	8c	66	96
4	7d	8d	61	92
5	7e	8e	83	94
6	7f	8f	-	36[c]

[a] Isolated yields starting from 1.0 equiv of **7**. [b] Isolated yields starting from 5.0 equiv of **7**. [c] 5 mol % of catalyst **1d** was used.

obtained in the presence of 10 equiv of cycloalkane[18b] or with the copper-catalyzed version involving the substrate as the solvent.[16a] Application of our methodology to linear alkanes was also found successful albeit to a lower extent, the product **8f** derived from 2-methylbutane being obtained in 36% yield (entry 6). It should be pointed out that the C−H functionalization here occurs, as in the case of adamantane, regioselectively at the tertiary position.

Kinetic Resolution of Sulfonimidamides. We have previously demonstrated that the high yields and selectivities obtained using our methodology are the consequence of a strongly matched effect between the chiral rhodium catalyst **1** and the sulfonimidamide **2**.[24] (*R*)-/(*S*)-Enantiomers of the benzylic C−H aminated products could thus be obtained via the combination of (*S*)-**1** and (*S*)-**2** or (*R*)-**1** and (*R*)-**2**, respectively. More interestingly, it was found that reaction between 1.0 equiv of (±)-**2a** and PhI(OCO*t*-Bu)$_2$ in the presence of 0.6 equiv of Indane and 3 mol % of [Rh$_2${(*S*)-nttl}$_4$] **1a** afforded the amino derivative (1*R*,*S*^{s})-**4c** in 45% yield (based on **2a**) with 92% de and 60% ee. Optimization of the reaction conditions then allowed us to observe that, by using catalyst **1d** and decreasing the amount of the iodine(III) oxidant to 0.55 equiv (with respect to **2a**), (1*R*,*S*^{S})-**4c** could be isolated in 46% yield, 98% de, and 98% ee, while sulfonimidamide (*R*)-**2a** was recovered in 42% yield and 97% ee. This experiment clearly demonstrates that kinetic resolution of sulfonimidamide **2a** is operating and meets most of the conditions of practicality.[41] In particular, this could circumvent the preparation of optically pure sulfonimidamides based on their resolution using chiral amines such as (*R*)-α-methylbenzylamine[22e] or (1*S*,2*R*)-norephedrine.[42] Kinetic resolution conditions were thus successfully applied to various benzylic substrates to give the corresponding C−H aminated products **4** in good yields in the 56−80% range (based on substrate **3**) and excellent diastereo- and enantioselectivities both generally greater than 97% (Table 7). Significantly, the results parallel those previously obtained with (*S*)-**2a** (Table 4), therefore illustrating the power of this kinetic resolution.

Mechanistic Considerations. The mechanism of the rhodium-catalyzed C−H amination is believed to occur via three elementary steps: (1) *in situ* generation of an iminoiodane from PhI(OCOR)$_2$ and the nitrogen-containing substrate, (2) formation of a rhodium−nitrene intermediate following oxidation of the rhodium(II) complex by the iminoiodane, (3) C−H insertion of the resulting metallanitrene (Figure 2).

Several studies by Du Bois, Che, and Müller have been dedicated to the elucidation of the overall pathway.[6d,13g,43] A combination of various physical data including isotope effects, Hammett analysis, and study of a radical clock suggests that a mechanism involving a direct concerted C−H insertion of a singlet rhodium-bound nitrene is operating.[43a,b] This conclusion has also been corroborated by a DFT computational study.[43c] The selectivities observed in the present diastereoselective intermolecular C−H amination parallel those observed by Du Bois[13g] and, therefore, led us to propose that a similar scenario should also occur with the sulfonimidamide-derived rhodium−nitrene species.[44,45] However, the hypothetical stepwise addition of a triplet metallanitrene via a H-abstraction/radical rebound pathway cannot be completely ruled out although the second step should be in this case extremely fast.[46]

As far as the formation of the iminoiodane is concerned (step 1), it has been postulated that the reaction involving a sulfamate as the nitrene precursor and PhI(OCO*t*-Bu)$_2$ is an equilibrium between starting materials and the iminoiodane.[13g] The data presented in the paragraph devoted to the kinetic resolution of sulfonimidamides corroborate this proposal. In particular, the limited amount of PhI(OCO*t*-Bu)$_2$ needed to perform the reaction together with the good yields (in the 56−80% range) and ee values of 97−99% obtained for products (1*R*,*S*^{S})-**4** demonstrate the existence of an equilibrium that may occur between enantiomeric iminoiodanes via ligand exchange. Since formation of 1.1 equiv of the racemic iminoiodanes A and B is

(41) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5−26. For other reviews dedicated to kinetic resolution, see: (a) Kagan, H. B.; Fiaud, J.-C. In *Topics in Stereochemistry*; Eliel, E. L., Fiaud, J.-C., Eds.; Wiley: New York, 1998; Vol. 18, pp 249−330. (b) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407−1446. (c) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974−4001.

(42) Toth, J. E.; Ray, J.; Deeter, J. *J. Org. Chem.* **1993**, *58*, 3469−3472.

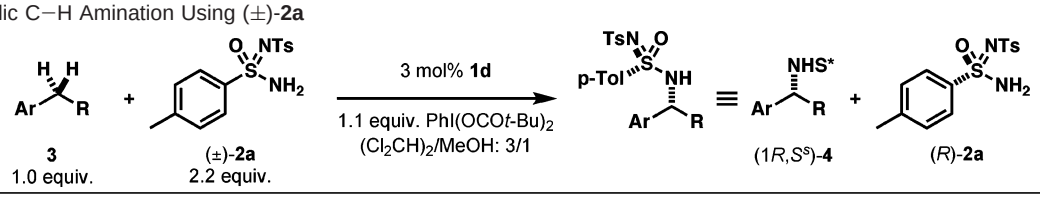
(43) (a) Nägeli, I.; Baud, C.; Bernardinelli, G.; Jacquier, Y.; Moran, M.; Müller, P. *Helv. Chim. Acta* **1997**, *80*, 1087−1105. (b) Du Bois, J. *Chemtracts: Org. Chem.* **2005**, *18*, 1−13. (c) Lin, X.; Zhao, C.; Che, C.-M.; Ke, Z.; Phillips, D. L. *Chem. Asian J.* **2007**, *2*, 1101−1108.

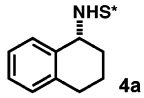
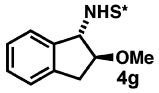
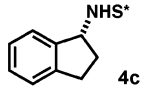
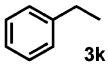
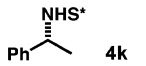
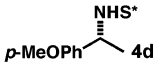
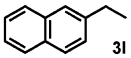
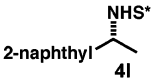
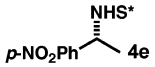
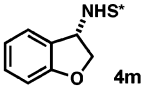
(44) C−H functionalization of secondary positions is favored since the latter offer the best compromise in terms of electronic and steric effects but insertion into activated primary positions (e.g., benzylic) or sterically accessible tertiary C−H bonds (as in adamantane) is also possible. Similar trends have been observed in the rhodium-catalyzed intermolecular C−H insertion of donor/acceptor carbenoids, the mechanism of which involves a concerted nonsynchronous insertion of a metallacarbene. Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861−2903.

(45) We tried to apply our procedure to (*R*)-2-phenylbutane and a cyclopropyl radical clock with the aim of demonstrating the nature of the mechanism. However, all our attempts have failed so far probably as a consequence of the sterically demanding reacting sites. Work is in progress to further investigate the exact nature of the intermediates.

(46) An H-abstraction/radical rebound mechanism has been invoked in the Ru(VI) porphyrin-mediated and the Mn(III) porphyrin-catalyzed amidations of alkanes. See: (a) Au, S.-M.; Huang, J.-S.; Yu, W.-Y.; Fung, W.-H.; Che, C.-M. *J. Am. Chem. Soc.* **1999**, *121*, 9120−9132. (b) Leung, S. K.-Y.; Tsui, W.-M.; Huang, J.-S.; Che, C.-M.; Liang, J.-L.; Zhu, N. *J. Am. Chem. Soc.* **2005**, *127*, 16629−16640. (c) Mahy, J.-P.; Bedi, G.; Battioni, P.; Mansuy, D. *New. J. Chem.* **1989**, *13*, 651−657.

Table 7. Benzylic C−H Amination Using (±)-**2a**



Entry	Substrate	Product	Yield[a]	de[b]	ee[b]	Entry	Substrate	Product	Yield[a]	de[b]	ee[b]
1	3a	 4a	67	97	99	5	3g	 4g	75	99	99
2	3c	 4c	77	98	98	6	 3k	 4k	57	98	97
3	3d	 4d	80	98	99	7	 3l	 4l	73	98	99
4	3e	 4e	56	88	99	8	 3m	 4m	77	88	99

[a] Isolated yields. [b] The de and ee values were determined by HPLC (Hypercarb or Symmetry Shield Column).

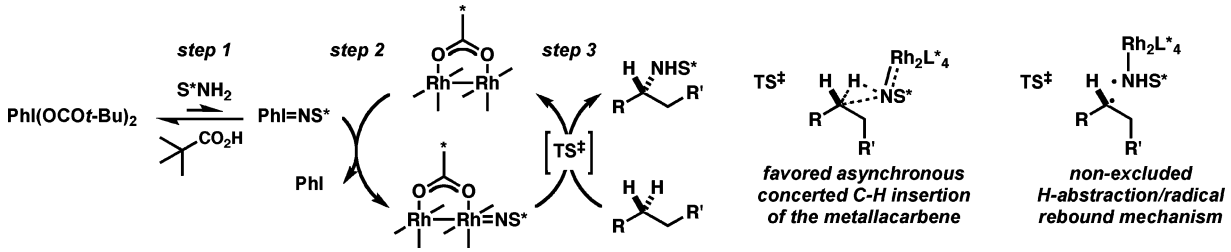


Figure 2. Presumed mechanism of the intermolecular catalytic C−H amination.

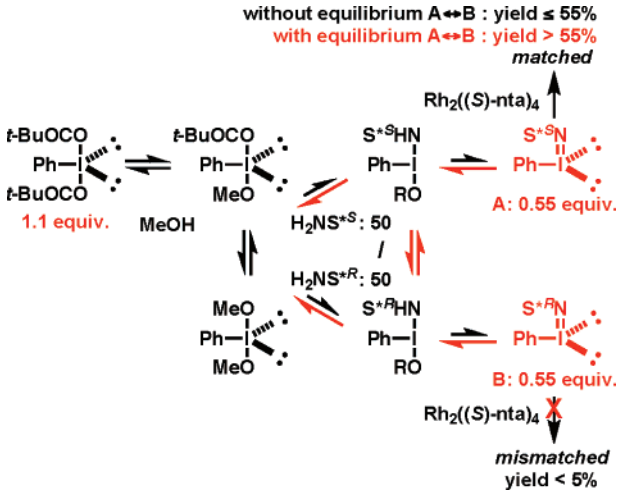


Figure 3. Possible reversible formation of iminoiodanes.

expected starting from 1.1 equiv of PhI(OCO*t*-Bu)$_2$ and 2 equiv of the racemic sulfonimidamide **2a** (Figure 3), no more than 55% of C−H aminated product **4** should thus be isolated if perfect kinetic resolution is operating in the absence of such a process.

The results displayed in Table 7 indicate that the yields are clearly above this limit: an equilibrium may take place between various substituted λ^3-iodanes via the favored associative pathway involving tetracoordinated species.[47,48] However, the origin of the strongly matched/mismatched effect between the (*S*)-rhodium catalyst and, respectively, the (*S*)- and (*R*)-sulfonimidamides is not well understood so far; work is in progress to elucidate the interactions involved in this recognition process.

Deprotection of the Sulfonimidoyl Group. Finally, cleavage of the sulfonimidoyl moiety was studied with the aim of developing reproducible conditions likely to be of general application. The use of sodium naphthalenide was previously reported by us to deprotect benzylic C−H aminated products without epimerization.[24] Recently, we have found a more general and convenient procedure involving introduction of a Boc group before removal of the sulfonimidoyl moiety with magnesium in methanol under sonication.[49] These conditions were successfully applied to benzylic and allylic products as well as to aminated alkanes (Figure 4). This reductive cleavage of the protecting group occurs in very good yields in the 86−92% range, the introduction of the Boc group being the limiting step in each case.

(47) The involvement of dicoordinated iodonium ions is unlikely because they would probably be coordinated by methanol, used here as a cosolvent, as soon as formed. Ochiai, M. *Top. Curr. Chem.* **2003**, *224*, 5−68.
(48) An analogous ligand exchange could explain the copper-catalyzed aziridination involving iodosylbenzene as the starting oxidant (see ref 12c) and the organocatalytic epoxidation described by Lee and MacMillan using an iminoiodane as a precursor of PhI=O. See: Lee, S.; MacMillan, D. W. C. *Tetrahedron* **2006**, *62*, 11413−11424.
(49) Xu, Y. M.; Shi, M. *J. Org. Chem.* **2004**, *69*, 417−425.

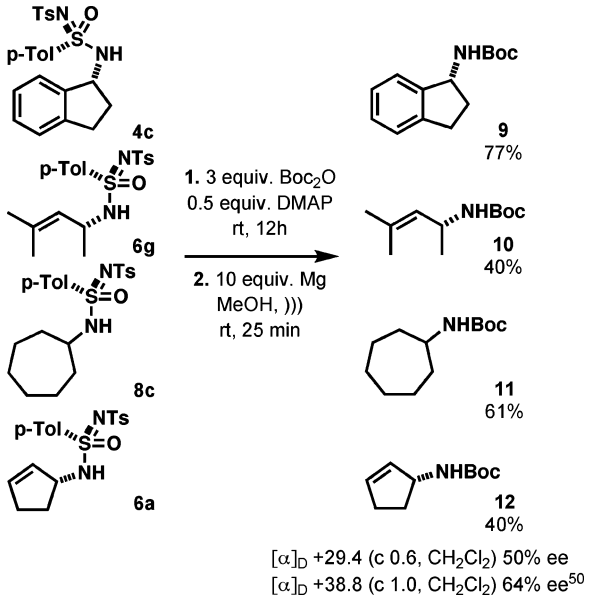


Figure 4. Deprotection of the C−H aminated products.

Transformation of the cyclopentenyl derivative **6a** by application of this sequence led to the *N*-(Boc)amine **12**. By comparison of its optical rotation with literature data,[50] the configuration at the allylic asymmetric center was shown to be (*R*). It should be mentioned that this sense of asymmetric induction parallels that observed with benzylic substrates.

Conclusion

We have developed a catalytic stereoselective intermolecular C−H amination of unprecedented scope involving C−H bond-containing substrates used in stoichiometric amounts. The transformation is based on the hypervalent iodine-mediated *in situ* generation of a chiral nitrene derived from sulfonimidamides of type **2**. Functionalization of benzylic and allylic substrates occurs with very high yields up to 92% and excellent stereoselectivities up to 99%. These remarkable reactivities and selectivities are the consequence of a strongly matched effect between the chiral rhodium catalyst [Rh_2{(*S*)-nta}$_4$] **1d** and optically pure sulfonimidamide **2a**, the power of which has been applied to stereoselective benzylic C−H amination involving kinetic resolution of racemic **2a**. Alkanes have also been found to react efficiently even under stoichiometric conditions, a result that paves the way to the use of these compounds as starting materials in organic synthesis. This methodology, which represents to the best of our knowledge one of the first for the intermolecular stereoselective catalytic functionalization of C−H bonds, may therefore find numerous applications in total synthesis.

(50) O'Brien, P.; Rosser, C. M.; Caine, D. *Tetrahedron* **2003**, *59*, 9779−9791.

Experimental Procedures

Typical C−H Insertion Procedure. In an oven-dried tube were introduced activated 4 Å molecular sieves (100 mg), Rh_2{(S)-nta}$_4$ **1d** (7.7 mg, 0.006 mmol), and (*S*)-(−)-*N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidamide (−)-**2a** (78 mg, 0.24 mmol). The tube was capped with a rubber septum and purged with argon. 1,1,2,2-Tetrachloroethane (0.75 mL) and methanol (0.25 mL) were added under argon, and the mixture was stirred for 5 min before addition of the substrate (0.2 mmol). The tube was cooled to −35 °C, and PhI(OCO*t*-Bu)$_2$ (115 mg, 0.28 mmol) was added. The mixture was stored in the freezer (−35 °C) for 3 days. After dilution with dichloromethane (3 mL), the molecular sieves were removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The oily residue was purified by flash chromatography on silica gel, affording the C−H insertion product.

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Supporting Information Available: Experimental details, characterization data, and spectra (^{1}H and ^{13}C NMR) for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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