Transition-Metal Catalysis

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Efficient Diastereoselective Intermolecular Rhodium-Catalyzed C–H Amination**

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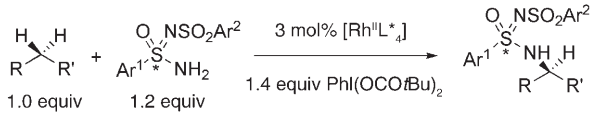
In memory of Pierre Potier

The selective functionalization of a C–H bond is an area of intense investigation as such a reaction leads to the formation of valuable building blocks from simple molecules.[1] Considering the ubiquity of C–H bonds in organic compounds, the search for a process that allows their selective transformation remains challenging. Methodologies have been recently developed for regioselective C–C,[2] C–O,[3] or C–N[4,5] bond formations that have found applications in total synthesis.[6]

In the case of C–H amination, significant results have been obtained by using transition-metal-catalyzed nitrene transfer that starts from iminoiodanes.[5,7] This field, pioneered by Breslow[8] and Mansuy,[9] has progressed considerably over the last five years with the discovery of new methodologies for the generation[5a,d,10] of these hypervalent iodine(III) reagents in situ. Thus, $PhI(OAc)_2$-mediated C–H amination has been shown to be catalyzed by ruthenium,[5a–c] manganese,[5a] rhodium,[5d–g] and silver[5i] complexes with sulfonamides, sulfamates, or carbamates as nitrene precursors. However, although the intramolecular process occurs efficiently, the intermolecular version suffers from low conversions or the need for a large excess of the starting alkane (5–100 equivalents) to obtain good yields.[1g,5a,b,h,11] The involvement of transition-metal catalysts has also allowed the development of enantioselective nitrene C–H insertions.[12] Although good enantioselectivities have been reported for intramolecular C–H aminations, an excess of alkane in the intermolecular version is again required to reach satisfactory selectivities.[12a,b,g] It is therefore in this context that we report herein an efficient diastereoselective intermolecular C–H amination that occurs under stoichiometric conditions and starts from an enantiomerically pure nitrene precursor (that is, (*S*)-*N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidamide (**1a**)).

We recently reported the generation of chiral iminoiodanes from sulfonimidamides in situ.[13] It was found that the nitrene intermediates generated from these chiral sulfur(VI) reagents are highly reactive species that add to various olefins in the presence of copper(I) catalysts to afford aziridines in good yields but with moderate diastereoselectivities.[13a] Rhodium(II) complexes have also been found to catalyze the aziridination of alkenes, and in particular the use of chiral ligands has been shown to improve diastereoselectivities.[13b] Given the greater ability of rhodium(II) tetracarboxylates to mediate C–H amination and the high reactivity of sulfonimidamide-derived nitrenes, we thus decided to combine these properties with the aim of developing an efficient intermolecular C–H amination (Scheme 1).

Initial experiments were aimed at screening various rhodium(II) complexes and enantiomerically pure substituted sulfonimidamides **1** in the presence of $PhI(OAc)_2$ and MgO in dichloromethane.[5d] We found that a combination of (−)-(*S*)-*N*-(*p*-toluenesulfonyl)-*p*-nitrobenzenesulfonimidamide (**1b**)[13a,b,14] and the chiral rhodium carboxylate catalysts



Scheme 1. Intermolecular C–H amination under stoichiometric conditions.

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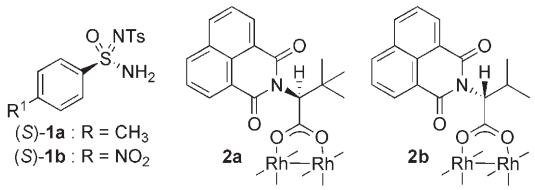
$[Rh_2\{(S)\text{-nttl}\}_4]$ (**2a**;[15] nttl = *N*-1,8-naphthoyl-*tert*-leucine; Scheme 2) gave good results with indane **3** as a model substrate. Starting with one equivalent of **3**, the *p*-nitro analogue of the C–H amination product **3a** was isolated in 45% yield and with >90% diastereoisomeric excess, as estimated by ^{1}H NMR spectroscopic analysis. However, when applied to other substrates, such as tetrahydronaphthalene **4**, these conditions led to lower yields.



Scheme 2. Structures of the *S* enantiomer of the sulfonimidamides **1** and of the rhodium catalysts **2**. Ts = tosyl.

Thus, we decided to study the influence of other reaction parameters. We were very surprised to observe that C–H amination with (*S*)-**1a** takes place in methanol, albeit in moderate yields.[16] A possible explanation is that methanol, contrary to dichloromethane, allows the solubilization of **1a**. We also discovered that the reaction works equally well in the absence of MgO. These observations prompted us to run the reaction in mixtures of CH_2Cl_2 and MeOH without a base. We thus found that a 1:3 mixture of MeOH/CH_2Cl_2 gives better conversions; consequently, compound **4a** could be isolated starting from tetrahydronaphthalene in 48% yield. Further improvements were obtained by replacing CH_2Cl_2 with 1,1,2,2-tetrachloroethane and $PhI(OAc)_2$ with the more soluble $PhI(OCOtBu)_2$.[17] The C–H amination product **4a** is formed in 80% yield with 96% *de* (Table 1, entry 2) under these conditions and at −35 °C.[18]

Application of this optimized procedure to electron-rich C–H bonds is particularly efficient (entries 1–6 and 8–11), whereas the reactivity drops slightly in the presence of an electron-withdrawing group, as observed with *p*-nitroethylbenzene (**8**) (entry 7). Therefore, except in the latter case, this stoichiometric intermolecular C–H amination leads to the formation of a single product in 62–93% yield with nearly complete diastereoselectivity (≥93% *de*).[19] These results, in terms of reactivity and selectivity, are superior to those reported so far, even in the presence of an excess of substrate.[1g,12] Moreover, with 2-methoxyindane (**11**), only the *trans* isomer **11a** was isolated in 62% yield with 99% *de*, as indicated by NOESY experiments (entry 10). This result illustrates the synthetic utility of the intermolecular C–H amination, as it stands in contrast to the intramolecular version that affords only the corresponding *cis* isomer.[5c–e,i]

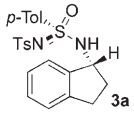
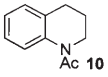
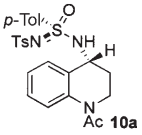
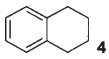
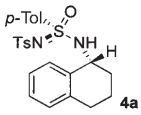
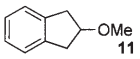
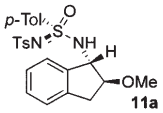
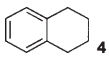
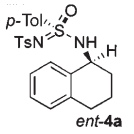
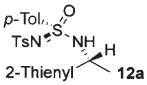
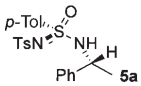
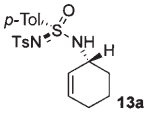
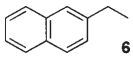
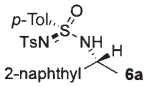
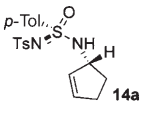
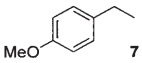
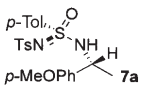
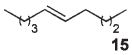
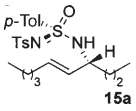
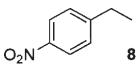
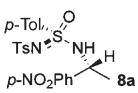
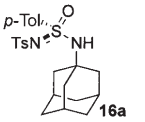
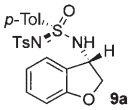
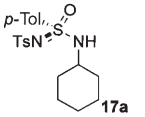
The high efficiency of this stereoselective C–H functionalization, which occurs with retention of configuration through a concerted nitrene insertion,[5d,20] is correlated to a dramatic matched effect between the chiral rhodium catalyst **2a** and the sulfonimidamide (*S*)-**1a**. On one hand, reaction of the latter with $[Rh_2(OAc)_4]$ leads to very poor conversions and selectivities. On the other hand, the mismatched combination of the enantiomer (*R*)-**1a** and catalyst **2a** gives *ent*-**4a** in only 10% yield with 53% *de*, whereas the same reaction starting from racemic **1a** affords **4a** in 33% yield with 97% *de*.[21] It should also be mentioned that the presence of methanol has a major influence on the matched effect. This result was applied to the preparation of *ent*-**4a**, obtained in 83% yield with 99% *de* (entry 3) from the matched combination of the sulfonimidamide (*R*)-**1a** and the rhodium catalyst $[Rh_2\{(R)\text{-ntv}\}_4]$ (**2b**; ntv = *N*-1,8-naphthoylvaline).[22]

Substrates with allylic C–H bonds were also studied to enhance the scope of the reaction. The reaction still occurred efficiently in 55–75% yield, but the diastereoselectivities were moderate (38–50%, entries 12–14). These results, however, compare favorably with those described in previous studies.[1g,12] More interestingly, competitive rhodium-catalyzed aziridination does not take place in the case of cyclohexene (**13**) and cyclopentene (**14**), contrary to previous reports of the use of sulfonamides and sulfamates[23] or of rhodium acetate with sulfonimidamides.[13b] This result is likely to be the consequence of the matched effect which favors C–H insertion as the reaction of racemic **1a** with the chiral catalyst **2a** affords a mixture of C–H amination product **13a** and aziridine in the case of cyclohexene. Finally, the high reactivity of the sulfonimidamide-derived nitrenes has been confirmed by application of the procedure to simple alkanes (entries 15 and 16). Adamantane **16** gives rise to the corresponding C–H insertion product **16a** in 69% yield, whereas the use of five equivalents of cyclohexane **17** affords **17a** in 65% yield, which is identical to the highest yield obtained so far with cyclohexane as the solvent.[5h]

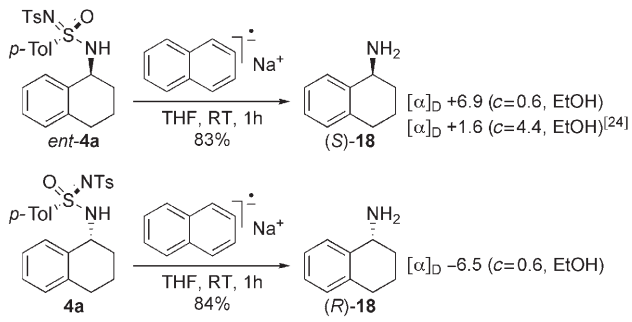
As both enantiomers of **1a** are resolved with (*S*)- or (*R*)-α-methylbenzylamine,[13a,b] the absolute configuration at the newly created asymmetric center for the C–H insertion product **5a**, and by analogy for **3a**–**12a**, was readily determined. Thus, the use of (*S*)-**1a** with rhodium catalyst **2a** leads to the *R* configuration at the benzylic center. This result was confirmed after removal of the sulfonimidoyl moiety from *ent*-**4a**. The free amine **18**, whose optical rotation corresponds to the *S* isomer,[24] was produced in 84% yield by using sodium naphthanelide in THF at room temperature; whereas, application of these conditions to **4a** afforded (*R*)-**18**, as indicated by the opposite optical rotation (Scheme 3). Importantly, chiral HPLC indicated that removal of the sulfonimidoyl group takes place without epimerization at the benzylic center.

In conclusion, we have discovered a highly efficient rhodium-catalyzed intermolecular C–H amination procedure with a sulfonimidamide as the nitrene precursor and the C–H-bond-containing substrate as the limiting component. This reaction occurs with good-to-excellent diastereoselectivities of up to 99%, particularly at secondary benzylic positions, and can be applied with equal success to the synthesis of both isomers of the resulting amine. The high reactivity and selectivity have been shown to be the consequence of a pronounced matched effect between the enantiomerically pure sulfonimidamide and the chiral rhodium catalyst. Such a procedure is of high interest for the total synthesis of natural products, for example, colchicine[25] or biologically active

Table 1: Intermolecular C–H amination with sulfonimidamide (*S*)-**1a** and catalyzed by $[Rh_2\{(S)\text{-nttl}\}_4]$ **2a**.[a]

Entry	Substrate	Product	Yield [%][b]	*de* [%][c]	Entry	Substrate	Product	Yield [%][b]	*de* [%][c]
1	 **3**	 **3a**	88	>99	9	 **Ac 10**	 **Ac 10a**	62	99
2	 **4**	 **4a**	80	96	10	 **OMe 11**	 **OMe 11a**	62	99
3	 **4**	 ***ent*-4a**	83[d]	99[d]	11	 **12**	 **2-Thienyl 12a**	78	98
4	 **5**	 **Ph 5a**	73	97	12	 **13**	 **13a**	75	38
5	 **6**	 **2-naphthyl 6a**	87	96	13	 **14**	 **14a**	72	50
6	 **MeO 7**	 ***p*-MeOPh 7a**	93	98	14	 **15**	 **15a**	55	50
7	 **8**	 ***p*-NO_2Ph 8a**	51	80	15	 **16**	 **16a**	69	–
8	 **9**	 **9a**	80	93	16	 **17**	 **17a**	65[e]	–

[a] All reactions were conducted at −35 °C in $Cl_2CHCHCl_2$/MeOH (3:1) with (*S*)-**1a** (1.2 equiv), $PhI(OCOt\text{-}Bu)_2$ (1.4 equiv), and **2a** (3 mol%). [b] Yield of the isolated products. [c] The *de* values were determined by HPLC (Hypercarb or Symmetry Shield Column). [d] *ent*-**4a** was obtained using 3 mol% of $[Rh_2\{(R)\text{-ntv}\}_4]$ (**2b**) and 1.2 equivalents of (*R*)-**1a**. [e] With 5.0 equivalents of cyclohexane.



Scheme 3. Deprotection of the C–H insertion products under reductive racemization-free conditions.

compounds, such as sertraline.[26] Studies are in progress in this area.

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Keywords: amination · C–H insertion · hypervalent iodine · nitrenes · rhodium

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