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Rhodium-catalyzed intermolecular C–H amination of simple hydrocarbons using the shelf-stable nonafluorobutanesulfonyl azide†

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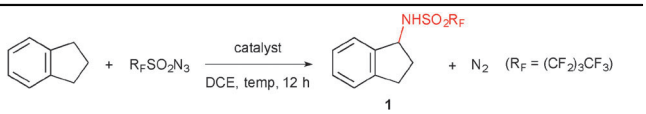
A new procedure has been developed for the direct intermolecular C–H amination of simple hydrocarbons using shelf-stable nonafluorobutanesulfonyl azide in the presence of a dirhodium(II) tetracarboxylate catalyst under mild reaction conditions. Some mechanistic details are briefly discussed on the basis of control experiments.

The direct chemoselective transformation of unactivated sp^3-hybridized C–H bonds into C–N bonds has emerged as a powerful tool in organic chemistry and the chemical industry that can streamline chemical synthesis by saving functional group transformations (such as hydroxyl to amine) and protection–deprotection steps.[1] Typical aminating reagents used for this purpose are high-energy species bearing electron-deficient N-substituents and capable of generating multiple bonds between late transition metals and nitrogen, such as iminoiodinanes (often prepared *in situ*), *N*-haloamines, and azides. Intra- and intermolecular protocols have been described based on Mn,[2] Fe,[2c,3] Ru,[2b,4] Co,[2c,5] Rh,[3a,6] Ir,[4b,7] Ni,[2c] Pd,[8] Cu,[1c,9] Ag,[10] Au,[11] and Zn[12] catalysts, including asymmetric versions,[2b,4b,6d,f,7] as well as under metal-free[13,14] conditions. In most of these transformations the reactive species is believed to be a (metal-)nitrene intermediate, which regioselectively inserts into the most electron-rich C–H bond unless steric factors contravene.

The use of azides is particularly appealing in this context since the reaction is highly atom-efficient and environmentally friendly, producing only gaseous nitrogen as a by-product and not requiring the addition of an oxidant. Polyfluoroalkanesulfonyl azides are the most electrophilic among organic azides, but have been very scarcely used in amination reactions[13e,15] probably due to the highly hazardous nature of their simplest and most typically employed representative, triflyl azide (TfN_3).[16] However, it has been recently shown that the higher molecular weight analog nonafluorobutanesulfonyl azide (NfN_3) is a more efficient, shelf-stable and economic reagent in diazo-transfer reactions[17] and other useful transformation mediated by TfN_3.[17f,18] In connection with our recent studies on new synthetic applications of NfN_3,[17b–d,f] here we describe how this reagent can perform the C–H amination of simple hydrocarbons under mild thermal conditions in the presence of a metal catalyst.

We selected indane as a model substrate for an initial screening of reaction conditions using 1.2 equivalents of NfN_3 (Table 1). No reaction occurred under simple thermal conditions in 1,2-dichloroethane (DCE) at 90–110 °C (below the reported decomposition temperature of NfN_3 of *ca.* 120 °C)[13e] for 12 hours in the absence of a metal catalyst (entry 1). After testing several transition metal salts (5 mol%) (entries 2–5), we found that dirhodium(II) tetracarboxylates promoted the reaction smoothly to afford the nonafluorobutanesulfonamide **1** in good isolated yields (entries 6, 12 and 13). The amination took place exclusively at the benzylic carbon. Only a marginal improvement in product yield was obtained with the more active $Rh_2(esp)_2$ catalyst (entry 13).[6c] A decrease in the reaction temperature had a dramatic deleterious effect, the reaction becoming sluggish below 70 °C (entries 7 and 8). Catalyst loadings as low as 1 mol% could be employed at the expense of a reduced,

Table 1 Development of the intermolecular sulfamidation reaction



1

Entry	Catalyst (mol%)	Temp (°C)	Yield[a] (%)
1	None	90–110	n.r.[b]
2	$Cu(OTf)_2$ (5)	90	n.r.
3	CuBr (5)	90	n.r.
4	$Pd(OAc)_2$ (5)	90	n.r.
5	AgOTf (5)	90	n.r.
6	$Rh_2(OAc)_4$ (5)	90	83
7	$Rh_2(OAc)_4$ (5)	50	<5
8	$Rh_2(OAc)_4$ (5)	70	20
9	$Rh_2(OAc)_4$ (3)	90	82
10	$Rh_2(OAc)_4$ (1)	90	63
11[c]	$Rh_2(OAc)_4$ (5)	90	75
12	$Rh_2(O_2CC_7H_{15})_4$ (5)	90	80
13	$Rh_2(esp)_2$ (5)	90	84

[a] Isolated yield. [b] No reaction. [c] Two equivalents of NfN_3 were used.

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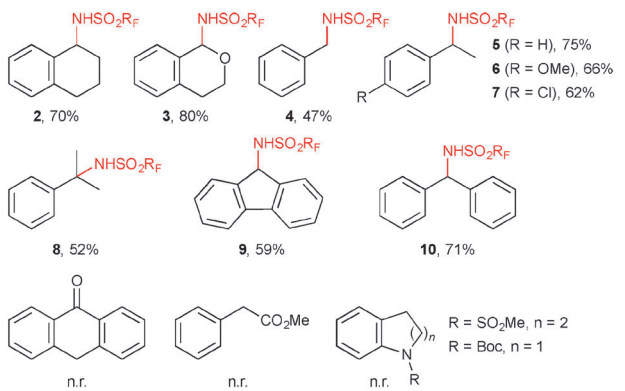
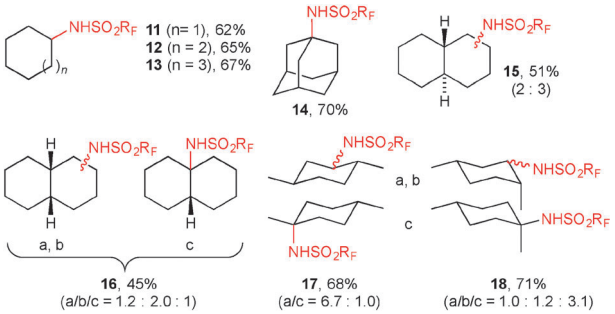
but still synthetically useful, amination yield (entry 10). Use of an excess of NfN_3 (2 equivalents) resulted in a slightly reduced product yield without formation of polyaminated products or imine[5a,9c] (entry 11). Optimum results were obtained at 90 °C employing a 3–5 mol% of catalyst and 1.2 equivalents of NfN_3 (entries 6, 9, 12 and 13).

We next examined the substrate scope under the cost-efficient optimized conditions using 5 mol% $Rh_2(OAc)_4$ at 90 °C in DCE. Simple aromatic compounds bearing primary, secondary or tertiary benzylic hydrogens where regioselectively monosulfamidated at the benzylic position with moderate to good isolated yields (47–80%) (Scheme 1). Amination of the aromatic ring was never observed under the employed experimental conditions.[13a,15a,19] In the case of isochromane, the reaction occurred exclusively at the ethereal benzylic carbon (compound **3**). However, in contrast to related Rh(II)-catalyzed amination reactions of aliphatic C–H bonds with aryl azides,[6i] no reaction was observed for substrates bearing carbonyl, ester, carbamoyl or sulfonamido groups, the starting compound being recovered unchanged after heating at 90 °C for 16 h (Scheme 1, last row).

Encouraged by these results, we next examined the scope of the transformation on simple hydrocarbon substrates bearing no functional groups (Scheme 2). Moderate to good isolated yields (45–70%) of monosulfamidated products were obtained under the previous optimized conditions using the hydrocarbons as limiting reagents (**14–18**) or as solvents (**11–13**). In the case of adamantane, amination took place regioselectively at the tertiary C–H bond, with no product arising from methylene amination being detected in spite of the 3 : 1 statistical preference for insertion at the methylene C–H bonds in this molecule. In contrast, *trans*-decalin was aminated exclusively at the methylene carbons, yielding an inseparable 2 : 3 mixture (determined from the ^{1}H NMR of the crude) of two regio- or stereoisomers (**15**). The larger steric encumbrance of the axially oriented methine hydrogens probably explains this selectivity. Thus, in *cis*-decalin an inseparable mixture of three regio- and/or stereo-isomeric sulfonamides (**16**) was formed showing that amination at the now more accessible methine carbon has taken place. The strong signal overlap observed in the ^{1}H NMR of the decalin reaction products impeded their stereochemical assignment.[9f] A similar change in 2°–3° site selectivity was observed for *cis*- and *trans*-1,4-dimethylcyclohexane. While the *cis*-isomer reacted preferentially



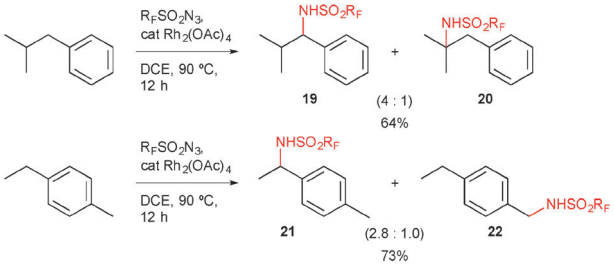
Scheme 1 Intermolecular amination of benzylic C–H bonds.



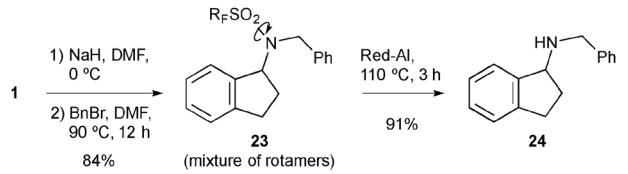
Scheme 2 Intermolecular amination of simple cyclic alkanes.

at the methylene carbons to afford an inseparable 6.7 : 1 mixture of 2°–3° sulfonamides **17** as single (unassigned) diastereoisomers, the *trans*-isomer gave a 2.2 : 3.1 mixture of 2°(2 diastereoisomers)–3°(single diastereoisomer) sulfonamides **18**, respectively, in spite of the 4 : 1 statistical preference for insertion at the methylene C–H bonds in this molecule, indicating again the preferential amination of the more accessible equatorially oriented methine C–H. We next studied the regioselectivity of the reaction in isobutylbenzene and 1-ethyl-4-methylbenzene (Scheme 3). The observed reactivity ratio for amination at benzylic *vs.* tertiary alkylic and at primary *vs.* secondary benzylic C–H bonds were, respectively, 2 : 1 and 4.2 : 1 (statistically corrected), which follow the trend of their expected relative C–H bond dissociation energies [BDE(Me_3C–H) = 96.5 kcal mol^{-1}; BDE($PhCH_2$–H) = 89.8 kcal mol^{-1}; BDE(PhCH(Me)–H) = 85.4 kcal mol^{-1}].[20]

A modest primary kinetic isotope effect (KIE, k_H/k_D = 2.47 at 90 °C; see ESI†) was measured for methylene C–H bond amination in a competition reaction using a 1 : 1 mixture of cyclohexane and cyclohexane-d_{12} and a limiting amount of NfN_3. This value is considerably lower than those previously reported for reactions proceeding *via* a triplet nitrene C–H abstraction/radical rebound amination mechanism (k_H/k_D > 5–6),[1a,4a] but it is in the same range as those evaluated for analogous rhodium-catalyzed C–H aminations (KIE = 1.2–2.6)[1d] proposed to proceed *via* concerted asynchronous singlet nitrene insertion. In line with this observation is that the tertiary sulfonamides **17c** and **18c** were diastereoisomerically different (see ESI†)[14d] suggesting that the amination took place with retention of configuration, which can rule out a radical stepwise mechanism. Based on these results, a concerted asynchronous pathway can be reasonably proposed for the present nitrene C–H insertion with only partial C–H bond breaking in the transition state.



Scheme 3 Competitive benzylic *vs.* tertiary alkylic and primary *vs.* secondary C–H bond amination.



Scheme 4 N-alkylation/reductive deprotection of sulfonamides.

The sulfonamide products could be further transformed taking advantage of the known reactivity of polyfluoroalkanesulfonamides.[21] Thus, N-alkylation could be readily performed by reaction of the sulfonamide anion with an alkyl halide (Scheme 4). The resultant *N*,*N*-disubstituted nonafluorobutanesulfonamide showed restricted rotation around the S–N bond, which caused a considerable broadening of the ^{1}H NMR signals at room temperature.[22] Subsequent treatment with Red-Al in toluene under thermal conditions afforded the corresponding N-alkylated amine in very good yield. This efficient two-step process can allow simple access to a variety of secondary amines, thus widely expanding the synthetic potential of the present C–H bond amination approach.

In summary, we have reported a new intermolecular C(sp^3)–H amination of simple hydrocarbons using the shelf-stable nonafluorobutanesulfonyl azide in the presence of a dirhodium(II) tetracarboxylate catalyst. The amination products were obtained in moderate to good yields and could be further transformed to secondary amines *via* a simple two-step process. Possible mechanistic pathways for the amination process were briefly discussed on the basis of control experiments.

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