Benzylic and Allylic Amination

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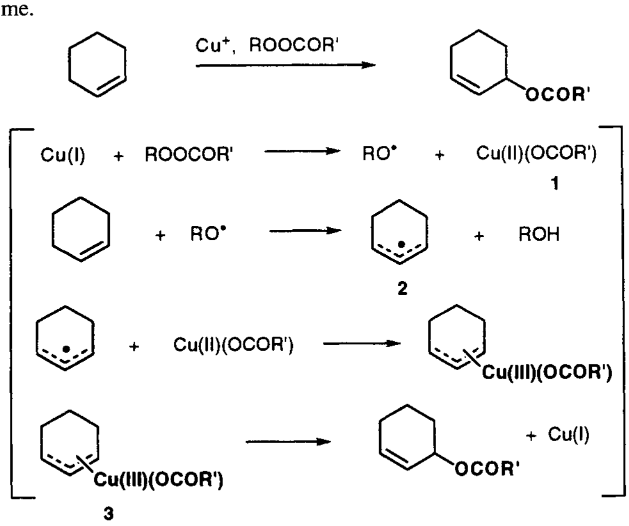
Abstract: *N*-(*p*-Toluenesulfonyl)amino group can be directly introduced at allylic or benzylic carbon by treating alkenes or alkylarenes with *t*-butyl *N*-(*p*-toluenesulfonyl)peroxycarbamate in the presence of Cu(II) triflate.

Allylic and benzylic amines are compounds widely used in organic synthesis and much effort has been directed toward this area of chemistry. As the results, several efficient methods have been developed, especially for the direct allylic amination of alkenes. Most of these allylic amination reactions belong to ene-type reaction,[1)] which is hardly extended to benzylic amination. Other allylic or benzylic amination reaction is nitrene insertion reaction but it often competes with aziridination reaction when the substrate is an alkene.[2)] Still, the substitution of allyl and benzyl halides or alcohol derivatives by an amine or its equivalent is a general method for the preparation of these classes of compounds.[3)] On the other hand, allylic hydroxylation can be effected in a single step by various methodologies.[4)] Among the methods, Kharash-Sosnovsky reaction which is a well-known method for allylic oxidation of alkenes (Scheme 1),[5)] drew our attention, because it is a metal-catalyzed reaction and therefore it can be carried out in an enantioselective manner if an appropriate optically active catalyst is available.[6)] This reaction starts with the formation of alkoxy radical and Cu(II)-carboxylate species (**1**) and proceeds through a radical (**2**) and a copper species (**3**). Iron-porphyrin or Mn-salen catalyzed benzylic hydroxylation has also been reported to proceed through a radical intermediate.[7)] Therefore, it seems reasonable to expect that direct amination of alkenes and alkylarenes can be realized, if an alkoxy radical and Cu(II)(NRR') species are generated at the same time.



Scheme 1

In the case of Kharash-Sosnovsky reaction, these two species are generated by the reaction of Cu(I) or Cu(II) species and alkyl peroxycarboxylate. On the other hand, carbamic acid is known to equilibrate with amines and carbon dioxide (Eq. 1). Thus, the reaction of Cu(I) and alkyl peroxycarbamate is expected to give an alkoxy radical and the desired Cu(II)(NRR') species (Eq. 2), which may enable the direct amination of allylic and benzylic carbons.

$$\mathrm{HOCONRR'} \rightleftharpoons \mathrm{CO_2} + \mathrm{HNRR'} \qquad (1)$$

$$\mathrm{Cu(I)} + \mathrm{ROOCONRR'} \longrightarrow \mathrm{RO^{\bullet}} + \mathrm{Cu(II)(NRR')} + \mathrm{CO_2} \qquad (2)$$

To explore this possibility, we first examined the benzylic amination of indan in the presence of Cu(I) triflate using *t*-butyl *N*-(*p*-toluenesulfonyl)peroxycarbamate in dichloromethane. The desired reaction occurred but the yield of 1-[*N*-(*p*-toluenesulfonyl)amino]indan was insufficient (Table 1, entry 1). We also examined *t*-butyl *N*-phenylperoxycarbamate and *t*-butyl *N*-(*p*-bromophenyl)peroxycarbamate as oxidants but the yield of the desired product decreased (entries 2 and 3). We recently found that chiral Cu(II) species served as an effective catalyst for asymmetric allylic hydroxylation.[6d,h)] Thus, we examined the reaction in the presence of Cu(II) triflate and an improved yield was obtained (entry 4). In all these reactions, peroxycarbamate was consumed smoothly but its consumption was not directly proportional to the amount of the desired product. The major side product was *p*-toluenesulfonamide (53% in the reaction described in entry 4) and a trace amount of 1-(*t*-butoxy)indan was also detected. The mechanism of the formation of *p*-toluenesulfonamide is unclear.

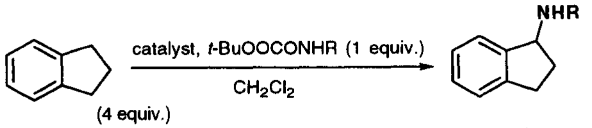
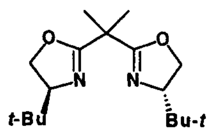


Table 1. Benzylic amination of indane using copper catalyst[a)]

Entry	Catalyst (equiv.)	Oxidant (R)	Time (h)	Temp.	Yield[b,c)] (%)
1	CuOTf (0.05)	*p*-toluenesulfonyl	5	rt	24
2	" (0.05)	phenyl	16.5	"	11
3	" (0.05)	*p*-bromophenyl	7	"	11
4	$Cu(OTf)_2$ (0.05)	*p*-toluenesulfonyl	5	"	34
5	$Cu(OTf)_2$-**4** (0.05)	"	22	"	35
6	$Cu(OTf)_2$-bipy[d)] (0.05)	"	85	"	37
7	$Cu(OTf)_2$ (0.1)	"	60	"	55
8	" (0.5)	"	60	"	56
9	" (1)	"	60	"	56
10[e)]	" (0.2)	"	7	85 °C	44

a) Reaction was carried out in the presence of MS 4A in dichloromethane.
b) Yield was calculated based on the amount of oxidant used.
c) Isolated yield.
d) bipy= 2,2'-bipyridine
e) Reaction was carried out without dichloromethane.



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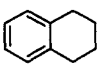
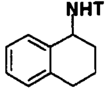
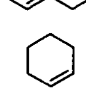
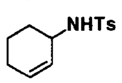
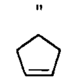
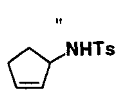
We next examined the reaction in various solvents such as toluene, dichloroethane, ethyl acetate, acetonitrile, acetone but dichloromethane was found to be the best among them. Use of polar solvents such as acetonitrile and acetone increased the formation of undesired *p*-toluenesulfonamide. We also examined the effect of copper catalyst and found that $Cu(OTf)_2$-bis(oxazoline) and $Cu(OTf)_2$-bipyridine complexes showed catalytic activity equal to $Cu(OTf)_2$ itself (entries 5 and 6). Increase of the amount of $Cu(OTf)_2$ improved the yield up to 55% yield, when 0.1 equivalent of $Cu(OTf)_2$ was used (entry 7). However, improvement was not observed any more, even if the amount of catalyst was further increased. The reaction at elevated temperature did not improve the yield (*c.f.* entries 7 and 10).

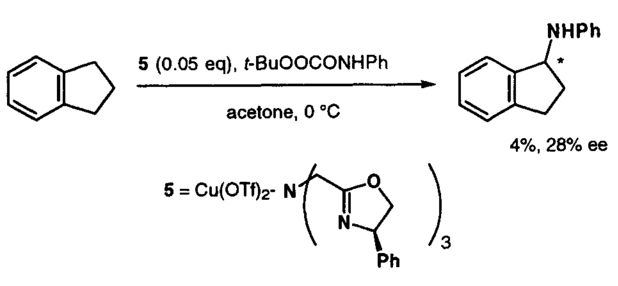
Under optimized conditions, we examined the amination of tetrahydronaphthalene and cycloalkenes (Table 2). Both benzylic and allylic aminations proceed as expected, but the amination of cyclohexene was slow and the formation of a large amount (74%) of *p*-toluenesulfonamide was observed, when the catalytic amount (0.1 equiv.) of $Cu(OTf)_2$ was used (entry 2). Use of stoichiometric $Cu(OTf)_2$ improved the yield to 58% (entry 3).

Table 2. Catalytic amination of alkylarene and alkenes[a)]

Entry	Substrate	$Cu(OTf)_2$ (equiv.)	Time (h)	Product	Yield[b)] (%)
1		0.1	60		45
2		0.1	60		27
3	"	1	4	"	58
4		0.1	60		53

a) Reaction was carried out in dichloromethane at room temperature with *t*-butyl *N*-(*p*-toluenesulfonyl)peroxycarbamate as an oxidant.
b) Isolated yield.

Asymmetric amination[8)] was also examined by using $Cu(OTf)_2$-**4** complex as a catalyst (Table 1, entry 5) but enantioselectivity was poor (3% ee),[9)] though yield was moderate. The same reaction in acetone showed a slightly improved enantioselectivity (7% ee) but the yield was low (3%). The reactions in acetone using *t*-butyl *N*-phenylperoxycarbamate as an oxidant also showed low enantioselectivity (7% ee, 3%). We next examined the reaction in the presence of $Cu(OTf)_2$-tris(oxazoline) complex **5**[6d,h)] at 0 °C (Scheme 2). Although the yield was poor, the modest enantioselectivity of 28% ee was observed, when *N*-phenylperoxycarbamate was used as an oxidant. The reaction using *N*-(*p*-toluenesulfonyl)peroxycarbamate as an oxidant did not proceed under these conditions.



Scheme 2

Preparation of *t*-butyl *N*-(*p*-toluenesulfonyl)peroxycarbamate[10)] and typical experimental procedure are as follows.

Preparation of *t*-butyl *N*-(*p*-toluenesulfonyl)peroxycarbamate: To *p*-toluenesulfonyl isocyanate (6.0 mL, 39.3 mmol) was added *t*-butyl hydroperoxide (5.9 N in toluene, 6.7 mL, 39.5 mmol) under nitrogen at room temperature and stirred for 18 h. To the mixture was added hexane (3.0 mL at a time) with vigorous stirring and the whole mixture was kept standing in a freezer. The resulting crystals (8.64 g, 77%) were collected by filtration. IR (KBr): 3300, 3260, 2988, 1763, 1596, 1410, 1354, 1198, 1178, 1148, 1090, 899, 839, 812, 745, 706, 671, 584, 550 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz): δ 8.43 (br, 1H), 7.96 (d, *J*=8.6 Hz, 2H), 7.36 (d, *J*=8.6 Hz, 2H), 2.45 (s, 3H), 1.31 (s, 9H).

Typical experimental procedure was exemplified by the benzylic amination of indan: To the mixture of pre-dried $Cu(OTf)_2$ (7.2 mg, 0.020 mmol), molecular sieves 4A (80 mg), and indan (94.6mg, 0.80 mmol) in CH_2Cl_2 (0.30 mL) was added *t*-butyl *N*-(*p*-toluenesulfonyl)peroxycarbamate (57.5 mg, 0.20 mmol, 1.0 eq) under nitrogen at room temperature. After being stirred for 60 h, the reaction mixture was directly subjected to column chromatography on silica gel (hexane/AcOEt= 9:1 to 4:1) to give 1-[*N*-(*p*-toluenesulfonyl)amino]indan as a colorless crystalline solid (31.8 mg, 55%). IR (KBr): 3257, 3067, 2948, 1736, 1597, 1481, 1458, 1421, 1319, 1159, 1099, 1063, 1034, 989, 918, 814, 750, 708, 669, 561 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz): δ 7.83 (d, *J*=8.2 Hz, 2H), 7.34 (d, *J*=7.9 Hz, 2H), 7.23-7.07 (m, 4H), 4.82 (dd, *J*=7.9, 7.3 Hz, 1H), 4.72 (d, *J*=8.6 Hz, 1H), 2.95-2.85 (m, 1H), 2.79-2.68 (m, 1H), 2.46 (s, 3H), 2.39-2.27 (m, 1H), 1.81-1.67 (m, 1H). Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87%. Found: C, 66.64; H, 6.00; N, 4.81%.

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(8) Quite recently, asymmetric amination of indan using $Rh_2[(R)\text{-}bnp]_4$ complex as a catalyst, was reported to show modest enantioselectivity of 31% ee (ref. 2d).

(9) The enantioselectivity was determined by HPLC analysis using chiral column (DAICEL CHIRALPAK AD; hexane/*i*-PrOH=9:1).

(10) *t*-Butyl *N*-(*p*-toluenesulfonyl)peroxycarbamate is an explosive substance. Therefore, full care must be taken when this oxidant is prepared and used in the laboratory.