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Nickel-Catalyzed Allylation of α-Amido Sulfones To Form Protected Homoallylic Amines

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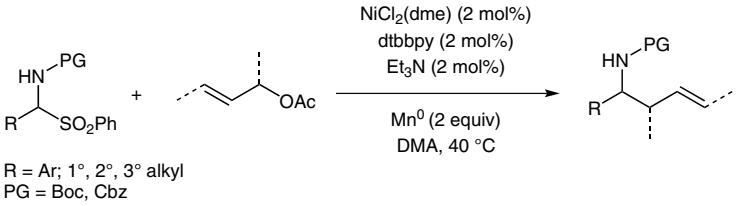

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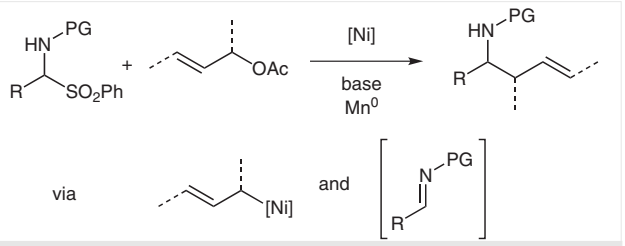
Abstract The allylation of stable, protected imine precursors, α-amido sulfones, with allylic acetates to form homoallylic amines is catalyzed by nickel under mild reducing conditions. Aliphatic and aryl imines are tolerated, as are substituted allylic acetates. In the case of substituted allylic acetates, high diastereoselectivity and regioselectivity is observed in some cases and the branched product is obtained almost exclusively.

Key words nickel, allylation, amines, imines, reduction

Homoallylic amines are useful synthetic intermediates due to their latent functionality. For example, homoallylic amines were key intermediates in the recent syntheses of (+)-preussin[1] and (–)-aphanorphine.[2] Despite this utility, fewer methods exist for the allylation of imines than for the analogous allylation of aldehydes.[3] The major challenges associated with imine allylation are the low reactivity of imines, competing decomposition of the imine, and the frequent need for a protecting/activating group on the nitrogen.[4] Aliphatic imines are particularly challenging to handle because of the potential for hydrolysis, and the most general strategies rely upon the use of more stable imines (sulfinyl imines, hydrazones) or synthesis and immediate use of less stable imines (*N*-Boc, *N*-Dpp, *N*-Ts).[5]

The majority of approaches have used allyl metal reagents (zinc,[6] silicon,[5,7] tin,[8] or boron[9]), either preformed or generated in situ, as the allyl donor. In some cases, highly enantioselective reactions have been developed. The use of allyl electrophiles has been limited to the use of allyl halides and stoichiometric indium[6b,9g,h,10] or palladium[11] catalysis with a diboron or indium reductant.[12] The cobalt-catalyzed allylation of *N*-aryl aryl imines with allyl acetate was reported by Gosmini,[13] but aliphatic imines were not explored.

Although it had previously been shown that the allylation of ketones[14] and, more recently, aldehydes[15] by allylic acetates could be catalyzed by nickel, the allylation of imines had not previously been reported. We present here a nickel-catalyzed allylation of aliphatic imines (Scheme 1) that starts from simple, stable precursors (allylic acetates and α-amido sulfones) and forms *N*-Boc and *N*-Cbz homoallylic amine products under mild conditions (40 °C, mild reductant, catalytic base). The imine is presumably generated in situ from the α-amido sulfone[16] by added base (Cs_2CO_3 or Et_3N) or by the $Mn(OAc)_2$ generated during the reaction (Table 1).

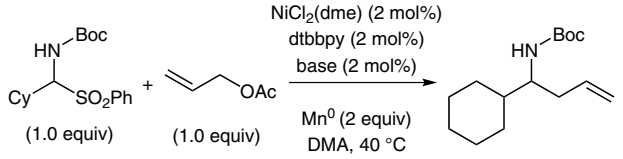


Scheme 1 Nickel-catalyzed allylation of α-amido sulfones

We began by exploring the use of stoichiometric amounts of base for imine formation (Table 1, entries 1 and 2). While cesium carbonate resulted in a higher yield at higher nickel catalyst loadings, at lower catalyst loadings triethylamine afforded equivalent yields (Table 1, entries 1–3). Even though the yield was slightly higher with stoichiometric cesium carbonate, we chose to focus on triethylamine due to its low cost and low molecular weight. The use of a catalytic amount of triethylamine resulted in no significant change in yield compared to stoichiometric triethylamine (Table 1, entries 3 and 4) and, when using allyl acetate, reactions proceeded in high yield without any triethylamine (Table 1, entry 5). However, reactions of more substituted allylic acetates conducted without added base took much longer to reach completion (data not shown). In addition, use of 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine resulted in a good yield for a reaction with simple allyl acetate, but poor yields for substituted allylic acetates (data not shown). An excess of allyl acetate improved yields slightly

(Table 1, entry 4 vs. 6) and the use of benzotriazole[17] as the leaving group instead of benzenesulfinate resulted in a lower yield (Table 1, entry 4 vs. 7). Finally, only trace amounts of product were formed in the absence of nickel, a ligand, or manganese (Table 1, entries 8–10). We chose to explore the scope of the reaction using the conditions reported in entry 6 (Table 1) due to the low catalyst loading that was achieved.

Table 1 Allylation of α-Amido Sulfones with Allyl Acetate



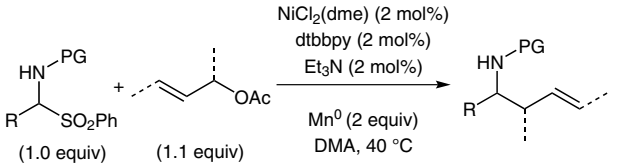
Entry	Modifications	Yield (%)[a]
1	10 mol% Ni and dtbbpy,[b] 1 equiv Cs_2CO_3	94
2	10 mol% Ni and dtbbpy, 1 equiv Et_3N	76
3	1 equiv Et_3N	89
4	2 mol% Et_3N	83
5	no Et_3N	93
6	1.1 equiv allyl acetate, 2 mol% Et_3N	88
7	benzotriazole substrate,[c] 2 mol% Et_3N	46
8	no Ni	1
9	no dtbbpy	1
10	no Mn^0	2

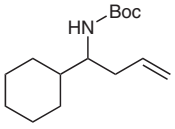
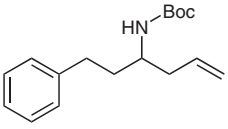
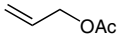
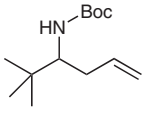
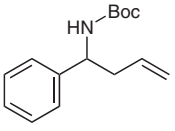
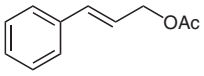
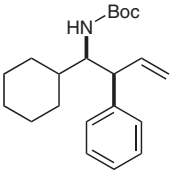
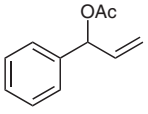
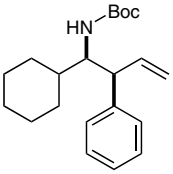
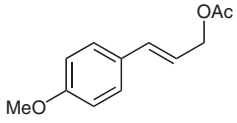
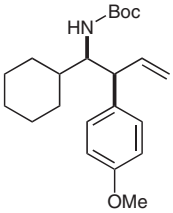
[a] Yields are corrected GC yields vs. internal standard (dodecane).
[b] 4,4′-Di-*tert*-butyl-2,2′bipyridine (dtbbpy).
[c] *tert*-Butyl {(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)(cyclohexyl)methyl}carbamate; ca. 7% (uncorrected GC yield) allyl acetate remaining at 48 h.

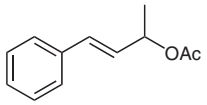
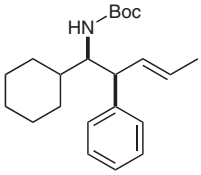
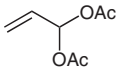
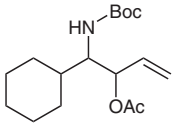
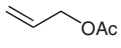
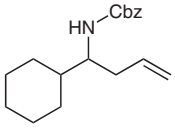
Application of these conditions to a variety of allylic acetates and α-amido sulfones is reported in Table 2. Alkyl α-amido sulfones substituted with primary and secondary alkyl groups adjacent to the nitrogen (R in Table 2) were allylated in high yield (Table 2, entries 1 and 2), but sulfones substituted with tertiary alkyl and aryl groups resulted in lower yield (Table 2, entries 3 and 4).[18] A number of substituted allylic acetates are tolerated (Table 2, entries 5–9).

In cases where a mixture of branched and linear homoallylic amines could be formed, the branched product was formed almost exclusively. The diastereoselectivity was excellent for cinnamyl acetate derivatives (Table 2, entries 5–8). The relative stereochemistry of the major product from cinnamyl acetate was determined to be *syn* by single-crystal X-ray analysis.[19] Similarly good regioselectivity and diastereoselectivity was obtained with 3-phenylbut-3-enyl acetate (Table 2, entry 8). Although 1,1-diacetoxyprop-2-ene also resulted in high diastereoselectivity (14:1 dr), the regioselectivity was lower (3:1 branched/linear, Table 2, entry 9). Crotyl acetate formed a 1:1 mixture of the *syn*- and *anti*-branched products (results not shown).[20]

Table 2 Substrate Scope for the Allylation Reaction

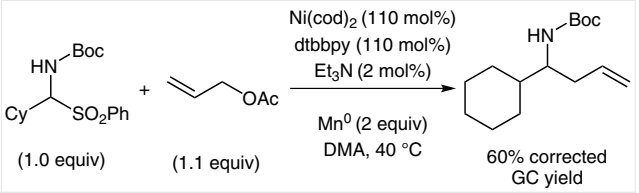


Entry	Allylic acetate	Product	Yield (%)[a]
1			85
2			87
3			49[b]
4			48[b,c]
5			75[d]
6			88
7			84[e]

Entry	Allylic acetate	Product	Yield (%)[a]
8			57[e]
9			77[f]
10			82

[a] Isolated yield after column chromatography (SiO_2).
[b] Low yield is due to dimerization of allyl acetate.
[c] The reaction did not reach full conversion after an extended reaction time.
[d] Relative configuration confirmed by single-crystal X-ray analysis.
[e] Relative configuration assigned by analogy to entry 5.
[f] The isolated product was obtained as a mixture of isomers. Based upon GC analysis, this mixture was a 14:5:1 ratio of major branched diastereomer/linear product/minor branched diastereomer.

Although we have not yet investigated the mechanism of this reaction in detail, it is clear from control experiments that nickel is required and it is likely that an *N*-Boc imine is formed in situ. This leaves two possible pathways: allylation of the imine by an allylnickel intermediate or nickel-catalyzed formation of an allylmanganese reagent that subsequently reacts with the imine. Two pieces of evidence support the allylnickel pathway. First, the reactions proceed in high yield in the presence of mild acids (NH, AcOH, $Et_3N{\cdot}AcOH$) with only one equivalent of allylic acetate, but allylmanganese reagents are sensitive to acid.[21] Second, a stoichiometric reaction of bis(cyclooctadiene)nickel(0) [$Ni(cod)_2$] and dtbbpy with α-amido sulfone, allyl acetate, and catalytic base, but no manganese formed the homoallylic amine product in 60% yield (Scheme 2). The preference for forming the same branched *syn* product from either the linear or the branched cinnamyl acetate suggests that the same allyl intermediate is involved in each reaction. We obtain the *syn* product with high selectivity, in contrast to recent results for the (PyBox)Ni-catalyzed allylation of aldehydes, where the *anti* product was observed.[15] Several stereochemical models have been proposed for the formation of *syn* products from the addition of allylmetal reagents to various imines, but further study is required to determine a stereochemical model for this transformation.[3,11a,22] While we have not explored the scalability of this reaction, we believe that this reaction could be scaled successfully based on our success scaling other cross-electrophile coupling reactions.[23]



Scheme 2 Stoichiometric allylation of an α-amido sulfone

In closing, we have demonstrated the first allylation of *N*-carbamoyl imines with allylic acetates.[24] The reaction works best with aliphatic imines, in contrast to the majority of other methods in the literature, and the use of α-amido sulfones avoids the handling of reactive imines. This report sets the stage for further development of stereoselective and even enantioselective reactions.[3a,15]

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379539.

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(18) We get substantially the same results with a preformed imine.

(19) Crystallographic data for the compound reported in Table 2, entry 5 has been deposited with the Cambridge Crystallographic Data Centre (CCDC 1022004). This data can be obtained free of charge from the CCDC at http://www.ccdc.cam.ac.uk/data_request/cif.

(20) Gong observed similar diastereoselectivity with crotyl acetate for the reductive allyation of aldehydes using nickel. See ref. 15.

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(24) **Typical Procedure for the Allylation of α-Amido Sulfones**

On the benchtop, an oven-dried 1-dram vial equipped with a Teflon-coated stir bar was charged with 4,4′-di-*tert*-butyl-2,2′-bipyridine (2.7 mg, 0.0100 mmol), $NiCl_2$(dme) (2.0 mg, 0.0100 mmol), *tert*-butyl cyclohexyl(phenylsulfonyl)methylcarbamate (177 mg, 0.500 mmol, 1.00 equiv), *N*,*N*-dimethylacetamide (DMA) (1.00 mL), a solution of cinnamyl acetate (91.8 µL, 0.550 mmol, 1.10 equiv in 1.00 mL DMA), Et_3N (1.40 µL, 0.0100 mmol), dodecane (10.0 µL), and Mn^0 (54.9 mg, 1.00 mmol). The reaction vial was then capped with a screw cap fitted with a PTFE-faced silicone septum and stirred (1200 rpm) at 40 °C. After 19 h, the reaction mixture was then filtered through a short silica pad (1.5 cm wide × 2 cm high), and the pad was washed with Et_2O (75 mL) before the filtrate was concentrated in vacuo. The residue was then purified by flash chromatography (hexanes–acetone, 95:5) to afford the pure homoallylic amine (Table 2, entry 5) as a white solid (124 mg, 75% yield). X-ray crystallography confirmed that the *syn* isomer was obtained; mp 101–103 °C. Due to the existence of rotamers at ambient temperature, the ^{1}H NMR spectrum was obtained at 55 °C: ^{1}H NMR (400 MHz, $CDCl_3$, 55 °C): δ = 7.28–7.15 (m, 5 H), 6.03 (dt, *J* = 17.1, 8.8 Hz, 1 H), 5.09–5.05 (m, 2 H), 4.06 (br s, 1 H), 3.86 (br s, 1 H), 3.43 (t, *J* = 8.2 Hz, 1 H), 1.29 (s, 9 H), 1.75–0.86 (series of m, 11 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.9, 141.6, 139.8, 128.5, 128.4, 126.5, 115.9, 78.8, 57.7, 52.9, 39.4, 31.2, 28.4, 28.3, 26.5, 26.4, 26.3. IR: 3341, 2924, 1678, 1535, 1173 cm^{-1}. LRMS (ESI$^+$): *m/z* = 352.3 [M + Na$^+$]. HRMS (ESI$^+$): *m/z* [M + H$^+$] calcd for $C_{21}H_{32}NO_2$: 330.243; found: 330.244. X-ray quality crystals were grown by slow evaporation of acetone.