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Nickel-Catalyzed Synthesis of Dialkyl Ketones from the Coupling of *N*-Alkyl Pyridinium Salts with Activated Carboxylic Acids

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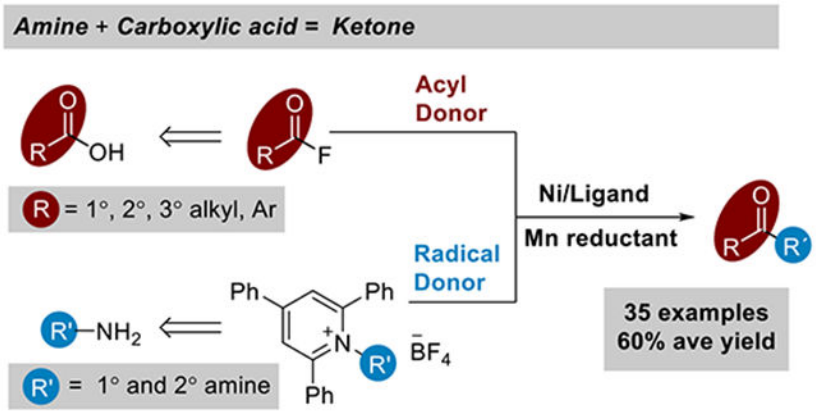
Abstract

While ketones are among the most versatile functional groups, their synthesis remains reliant upon reactive and low abundance starting materials. In contrast, amide formation is the most-used bond construction in medicinal chemistry because the chemistry is reliable and draws upon large, diverse substrate pools. A new method for the synthesis of ketones is presented here that draws from the same substrates used for amide bond synthesis: amines and carboxylic acids. A nickel terpyridine catalyst couples *N*-alkyl pyridinium salts with *in-situ* formed carboxylic acid fluorides or 2-pyridyl esters under reducing conditions (Mn metal). The reaction has broad scope, as demonstrated by the synthesis of 35 different ketones bearing a wide variety of functional groups with an average yield of 60 ± 16%. This approach is capable of coupling diverse substrates, including pharmaceutical intermediates, to rapidly form complex ketones.

Graphical Abstract



Keywords

Ketone Synthesis; Cross-Electrophile Coupling; Pyridinium Salts; Acyl Fluorides; Nickel Catalysis

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Supporting information for this article is given via a link at the end of the document.

Conflict of interest: The authors declare no conflict of interest.

The ketone functional group plays a central role in organic synthesis: it is present in many target molecules (natural products, drugs, materials), and is also a key intermediate in the synthesis of C-C bonds and alcohols.[1] However, the synthesis of ketones continues to rely upon methods that are limited in functional group compatibility and use starting materials of low abundance (Scheme 1). Ketones are most often synthesized by the addition of an organometallic reagent to an aldehyde followed by oxidation[1a] or, more recently, the coupling of an organometallic reagent to an activated ester.[2,3] This latter strategy is useful because there are many more alkanoic acids than aliphatic aldehydes, yet the organometallic coupling partner has limited availability and functional group compatibility.

In contrast, amide bond formation is among the most reliable coupling reactions.[4] A recent analysis ranked it as the most used reaction in medicinal chemistry, accounting for 25% of all reactions used in drug discovery. This is driven, in part, by the large numbers of amines and carboxylic acids that are commercially available.[5] A ketone synthesis that could utilize these substrate pools would dramatically increase easily available chemical space. In this vein, Matsuo recently reported an exciting advance: the cross-coupling of *N*-aroylsuccinimides with alkylpyridinium salts [6] This approach worked for benzoic acid derivatives, but was not useful for the larger alkanoic acid substrate pool.

We show here how recent developments in our two research groups can be combined to achieve a general synthesis of dialkyl ketones from alkyl amines and alkyl carboxylic acids (Scheme 1). On one hand, cross-electrophile[7] approaches to ketone synthesis have been developed to eliminate the need for organometallic reagents by coupling of activated esters (-Cl, -SPy, -OCO_2R) with alkyl halides[8] or, recently, a second carboxylic acid activated as an *N*-hydroxyphthalimide ester.[9] On the other hand, deaminative cross-couplings[10] of alkyl pyridinium salts have rapidly progressed, including cross-electrophile couplings with aryl halides.[11] We show here how these advances can be combined to form ketones from amines and carboxylic acid derivatives.[12,13]

The main challenge to realizing this transformation was achieving high cross-selectivity without resorting to a large excess of one coupling partner. Previous cross-electrophile couplings of alkyl pyridinium salts with aryl halides had shown that this balance of reactivity and selectivity could be challenging to achieve.[11] Based upon the hypothesis that the ketone product forms from the coupling of an acylnickel(II) intermediate with an pyridinium-salt-derived alkyl radical (Scheme 1),[8i,12e,14] we sought an acyl donor that would react quickly with the nickel catalyst, would not be easily reduced to form a radical, [15] and could be isolated or formed *in situ*.

Examination of activating strategies for carboxylic acids led us to acyl fluorides.[16] Acyl fluorides have several advantages: they can be made *in situ* (an advantage over *N*-acylimides or imides[17]), the liberated fluoride does not interfere with productive catalysis (a problem for thioesters[8d,8g]), and they can be purified if needed (unlike anhydrides or acid chlorides).

After systematic screening of different ligands, solvents, additives and reaction temperatures, we found optimal conditions for coupling an acyl fluoride with a primary alkyl pyridinium salt (Table 1): $NiCl_2$(dme), **L5**, and Mn in NMP at 60 °C. These conditions

provided ketone product **1** in 79% isolated yield (entry 1, Table 1). While 62-65% yields were obtained with electron-rich bipyridine ligands (**L1** and **L2**, entries 3-4), terpyridine and electron-poor bipyridine ligands were not effective for this transformation (See Tables S2.1-S2.4 in Supporting Information). In contrast to our previous reports [8d, 9b], the analogous *S*-2-pyridyl thioester (entry 7) or 2-pyridyl ester (entry 8) provided a low yield of product **1** and primarily formed the deaminative alkyl dimer 1,4-diphenylbutane. A lower yield was observed when switching the reductant from Mn to Zn (entry 9). This could be attributed to slower reduction of the catalyst[18] or direct reduction of pyridinium salts by Mn being important for product formation (entry 10).[19] Finally, purified acid fluoride could be replaced by *in-situ*-generated acid fluoride (entry 2). Among several methods tested, fluoro-*N*,*N*,*N*′,*N*′-bis(tetramethylene)formamidinium hexafluorophosphate (TFFH) with 1,8-bis(dimethylamino)naphthylene (proton-sponge) was the most useful.[16e] While *in-situ* activation of the carboxylic acid was successful, we obtained low yields with an unpurified pyridinium salt (22% NMR yield of 1 as in Table 1, entry 2).

We found that secondary alkyl pyridinium salts required modified conditions (Table 2 and Tables S2.5-S2.7 in Supporting Information). These secondary alkyl reagents typically undergo more facile C—N bond cleavage, making formation of dihydropyridine byproduct even more competitive.[11a] To avoid this byproduct, these changes were made: 1) using 2-pyridyl esters instead of acyl fluorides; 2) changing the solvent to THF and lowering the temperature; 3) switching the ligand to **L4** (entry 2). The use of $NiBr_2$(dme) and a slight increase in the amount of pyridinium salt, from 1.0 to 1.5 equiv, further increased the yield to 72% (entry 4).

The scope of these conditions is broad, as demonstrated by the 35 examples in Table 3. The majority of these examples used *in-situ* activation of the carboxylic acid, but in some cases purification of the product from proton-sponge-derived side products was difficult and pre-formed acyl fluorides were used. Pyridinium salts of unbranched and α-branched amines coupled well, but salts of tertiary carbinamines are not suitable substrates.[20] Primary, secondary, and tertiary carboxylic acids coupled in high yield, but a particularly hindered tertiary carboxylic acid, abietic acid, and α-amino acids coupled in low yield (see Supporting Information Table S5 for additional low-yielding substrates). Although not a focus of this study, in a preliminary result, a prototypical aryl carboxylic acid, naphthoic acid, could be coupled via its acid fluoride to give **35** in 41% yield, but a general solution to aroyl acids will require further optimization.[21] Finally, α-alkoxy carboxylic acids, a common motif found in cetirizine and other bioactive compounds,[22] could be coupled with slightly modified conditions (**29**, **30**).

Highlights of the functional group tolerance include basic amines (**4**, **19**, **20**, **21**, **27**, **28**, **29**, **30**, **32**), pyridine (**2**), cis-alkene (**34**), and even a dihydropyridine (**6**) that could deactivate a metal catalyst by coordination or be prone to oxidation under photoredox catalysis[23] or electrochemical conditions.[24] Acidic N-H bonds of Boc-β-alanine (**14**), a urea (**31**) or an *N*-aryl amide (**33**) as well as esters (**5**-**9**, **12**, **25**-**27**) and ketones (**10**, **11**, **13**) were tolerated, but would pose a problem for methods based upon organomagnesium or organolithium reagents.[2] Conveniently, the chemistry can be run preparatively on the benchtop (740 mg of **19**) and generally uses a 1:1 or 1:1.5 ratio of starting materials.

Although we have not yet studied the reaction mechanism, the similarities to other cross-electrophile coupling reactions[8i,12e,14] suggest an analogous mechanism: initial oxidative addition of the acyl fluoride to nickel(0)[16e] followed by radical addition to the resulting acylnickel(II) intermediate (Scheme 1). The resulting acyl-alkyl nickel(III) species could reductively eliminate ketone product. Formation of alkyl radicals from *N*-alkylpyridinium salts can be mediated by nickel or arise from direct reduction with manganese.[6, 10a, 10i, 11a, 11b, 11e] Another possibility is the reduction of an acylnickel(II) intermediate to form an acylnickel(I) species that can then react with pyridinium salts.[16g,25]

The ability to use carboxylic acids and amines as a substrate pool is valuable because these are two of the largest pools of commercially available alkyl fragments.[5] This flows from the reliance of medicinal chemistry on amide bond formation.[4] Indeed, alkyl amines are unique in that there are more listed for sale than reported in the literature![26] In some cases this translates to lower prices (see analysis in the Supporting Information), but it also means that complex amines and acids can be repurposed as starting materials, such as a mosapride intermediate (**19**-**21**, **27**-**29**, **32**), amlodipine (**6**), cetirizine (**30**), an atorvastatin intermediate (**33** and a side-chain fragment in **7**), biotin (**31**), and lithocholic acid (**32**). The ability to leverage these pools to make ketones instead of amides opens up new areas of chemical space with minimal effort, adding another dimension to the medicinal chemist's toolbox.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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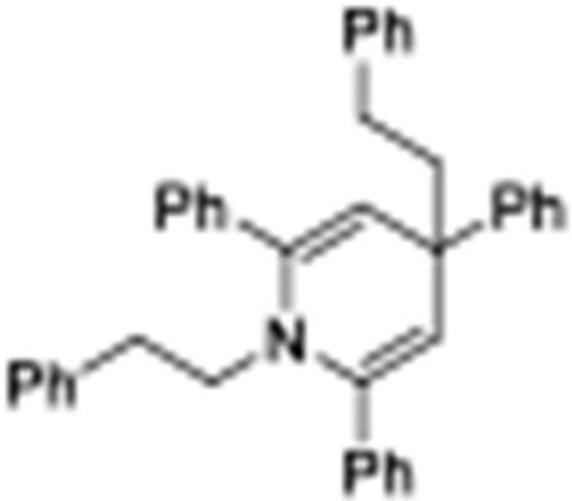
[19]. We have observed significant amount of dihydropyridine byproduct from crude NMR. The structure is consistent with our previous observed byproduct (see ref. 11a), and the structure was assigned to be:



[20]. Tertiary carbinamines cannot be converted into 2,4,6-triphenylpyridinium salts, except for cyclopropyl examples, presumably due to steric hindrance between the tertiary alkyl group and 2,6-phenyl groups.

[21]. At this time, reference [6] contains a more general, higher yielding route to aryl alkyl ketones from aryl carboxylic acids and amines.

[22]. A search of the REAXYS database for HO_2CCH_2OR found 22844 substances with pharmacological data. This includes pesticides such as 2,4-dichlorophenoxyacetic acid (2,4-D) and fluroxypyr as well as drugs such as treprostinil, aceclofenac, cefixime, cetirizine, and rifamycin B.

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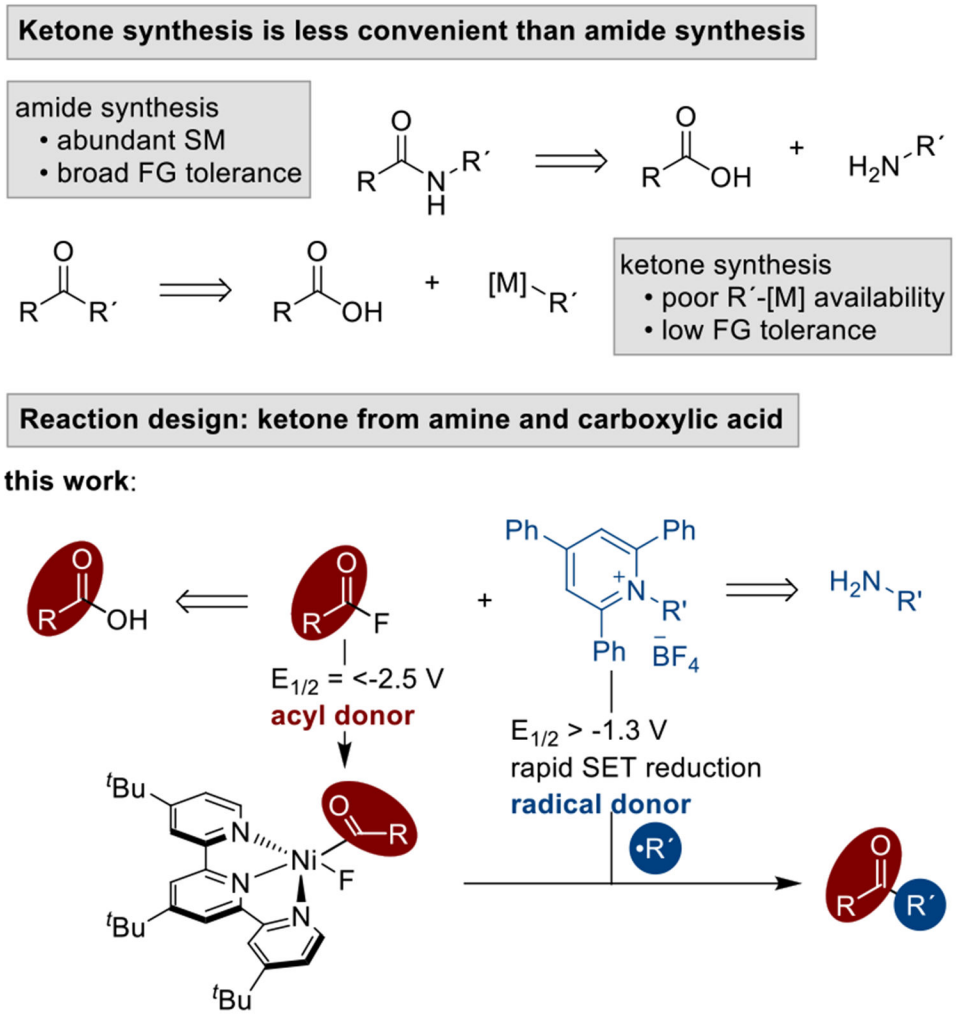
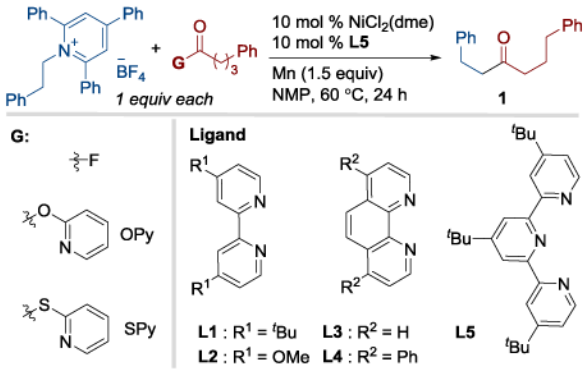
[26]. Alkyl-NH_2: 1.26 million in Beilstein Database, 1.40 million listed in eMolecules commercial availability database. Alkyl-Br: 308 thousand in Beilstein, 201 thousand in eMolecules. See also an analysis of substrate availability in the Supporting Information.



Scheme 1.
How to make ketones from amine and carboxylic acid derivatives.

Table 1.

Optimal conditions for primary pyridinium salts.



Entry[a]	Change in condition from scheme	G	1 (%)[b]
1	None	F	82 (79)
2[c]	In situ formation of acyl fluoride	F	75
3	**L1** instead of **L5**	F	62
4	**L2** instead of **L5**	F	65
5	**L3** instead of **L5**	F	53
6	**L4** instead of **L5**	F	41
7	Different **G**	SPy	4
8	Different **G**	OPy	11
9[e]	Zn instead of Mn	F	5
10[d]	No nickel	F	0
11[d]	No ligand	F	0
12[e]	No Mn reductant	F	0

[a] Pyridinium salt (0.125 mmol, 1 equiv), acyl fluoride (0.125 mmol, 1 equiv), $NiCl_2$(dme) (0.0125 mmol, 10 mol %), ligand (0.0125 mmol, 10 mol %), Mn (0.1875 mmol, 1.5 equiv) was stirred in NMP (0.8 mL) at 60 °C for 24 h.

[b] GC yield vs 1,3.5-trimethoxybenzene standard. Isolated yield in parentheses.

[c] Carboxylic acid (0.125 mmol, 1 equiv), TFFH (0.125 mmol, 1 equiv), 1,8-bis(dimethylamino)naphthylene (0.125 mmol, 1 equiv), NMP (0.8 mL).

[d] Significant amount of acyl fluoride recovered.

[e] Both starting materials recovered.

G = Activating Group.

Table 2.

Optimal conditions for secondary pyridinium salts.

Entry[a]	Change in condition from scheme	G	8 (%)[b]
1	None	F	14
2[c]	**L4** instead of **L5** in THF	OPy	61
3[c]	As entry 2, $NiBr_2$(dme) instead of $NiCl_2$(dme)	OPy	66
4[c]	As entry 3, 1.5 equiv of pyridinum	OPy	72

*[a]*Pyridinium salt (0.125 mmol, 1 equiv), acyl fluoride or 2-pyridyl ester (0.125 mmol, 1 equiv), $NiCl_2$(dme) (0.0125 mmol, 10 mol%), ligand (0.0125 mmol, 10 mol%), Mn (0.1875 mmol, 1.5 equiv) was stirred in corresponding solvent (0.8 mL) at 60 °C for 24 h.

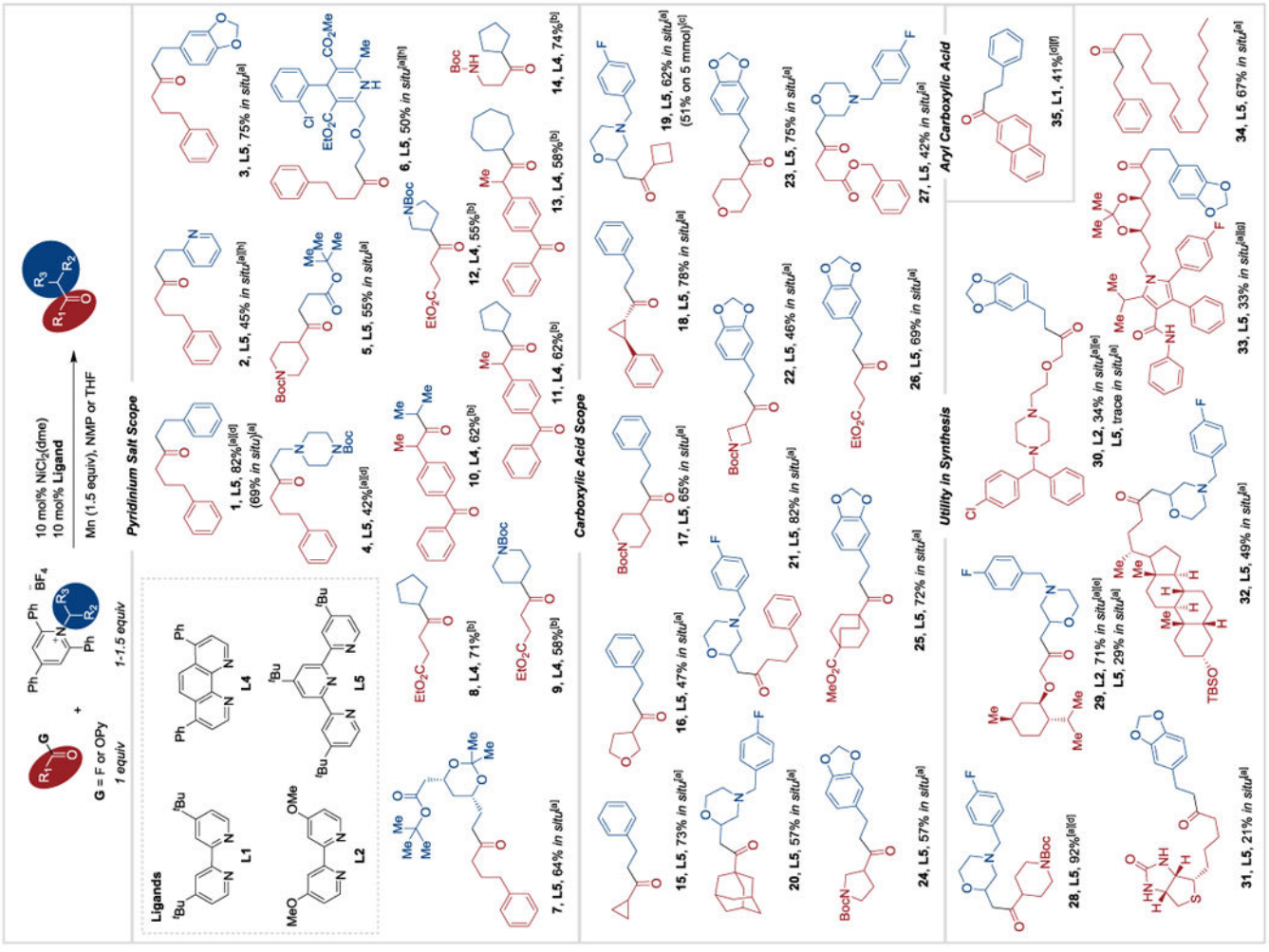
*[b]*GC yield vs 1,3.5-trimethoxybenzene standard.

*[c]*Reaction conducted at r.t.

G = Activating group.

Table 3.

Substrate scope for the deaminative coupling of pyridinium salts with carboxylic acid derivatives.



[a] After initial acid fluoride formation using carboxylic acid (0.5 mmol, 1 equiv), TFFH (0.5 mmol, 1 equiv) and proton sponge (0.5 mmol, 1 equiv), the coupling was run on 0.5 mmol scale with a 1:1 ratio of starting materials, ligand **L5** (0.05 mmol, 10 mol%), Mn (0.75 mmol, 1.5 equiv) in NMP (3 mL) at 60 °C for 24 h.

[b] Reaction run at 0.5 mmol scale using pyridinium salt (0.75 mmol, 1.5 equiv) and pre-formed 2-pyridyl ester (0.5 mmol, 1 equiv) with $NiBr_2$(dme) (0.05 mmol, 10 mol%), ligand **L4** (0.05 mmol, 10 mol %), Mn (0.75 mmol, 1.5 equiv) in THF at r.t. for 24 h.

[c] Reaction run on 5 mmol scale on benchtop, see Supporting Information.

[d] Pre-formed acyl fluoride was used.

[e] **L2** used instead of **L5**.

[f] **L1** was used instead of **L5**.

[g] Reaction run on 0.178 mmol scale at standard concentration.

[h] NMR yield shown. Product was not separated from impurities, see Supporting Information for details.

Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl.