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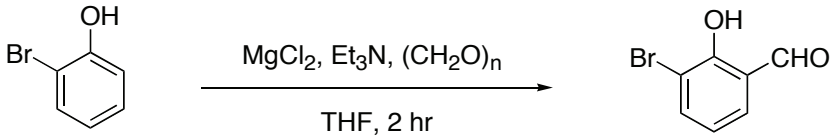
Discussion Addendum for: *ortho*-Formylations of Phenols; Preparation of 3-Bromosalicylaldehyde



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Several methods are available for the direct formylation of phenols, but most of them suffer from lack of regioselectivity. Moreover, several of the methods involve the use of noxious reagents and harsh reaction conditions resulting in moderate to good yields of aldehydes.[3] An exception is the formylation of phenols using the acceptable reagents $MgCl_2$, Et_3N and paraformaldehyde giving high yields of salicylaldehydes from reactions exclusively at the *ortho*-position.[4] Additional examples and applications of this method since its appearance in 1999 are presented here. We have emphasized the scope of the reaction and its participation in one-pot preparations.

Scope of the *ortho*-Formylation Reaction

Numerous applications of the formylation reaction have been reported in the past twelve years. A number of substituted phenols have been successfully formylated (Figure 1). Alkyl and alkoxy substituents promote the formylation, with high to excellent yields of salicylaldehydes being obtained (Figure 1).[4,5] Highly substituted phenols undergo the reaction; for example, reaction of the phenol **1** furnished the salicylaldehyde **2** in 62% yield.[6] Surprisingly, however, α,ω–*bis*(*p*-hydroxyphenyl)alkanes were unreactive towards the method.[7]

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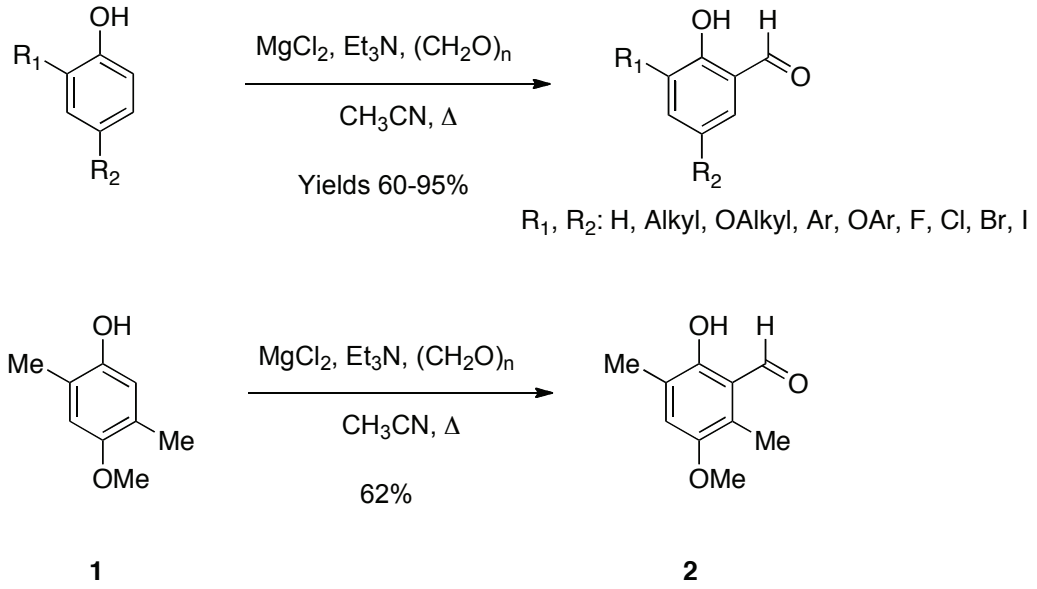

Figure 1. *Ortho*-formylation of phenols using $MgCl_2$, Et_3N and para-formaldehyde.

The method has been used for the formylation of estrogens.[8,9] The reactions occurred to provide excellent yields of regioisomeric aldehydes, with high preference for the 2-isomer (Table 1, Figure 2).

Table 1. Results from *ortho*-formylation of estrogens.

R_1	R_2	R_3	Regioisomeric ratio of 2- and 4-isomers	Yield %
OH	H	H	13:1	92
OH	CCH	H	6:1	86
OH	CH_2CH_3	H	12:1	90
H	OH	H	13:1	85
OAc	H	H	8:1	90
OH	H	OH	not determined	15
=O		H	9:1	90
OCH_2CH_2O		H	12:1	74

The practical use of this method was demonstrated with the synthesis of the anti-cancer agent 2-methoxyestradiol (**3**) from estradiol in 36% overall yield (Figure 2).[9]

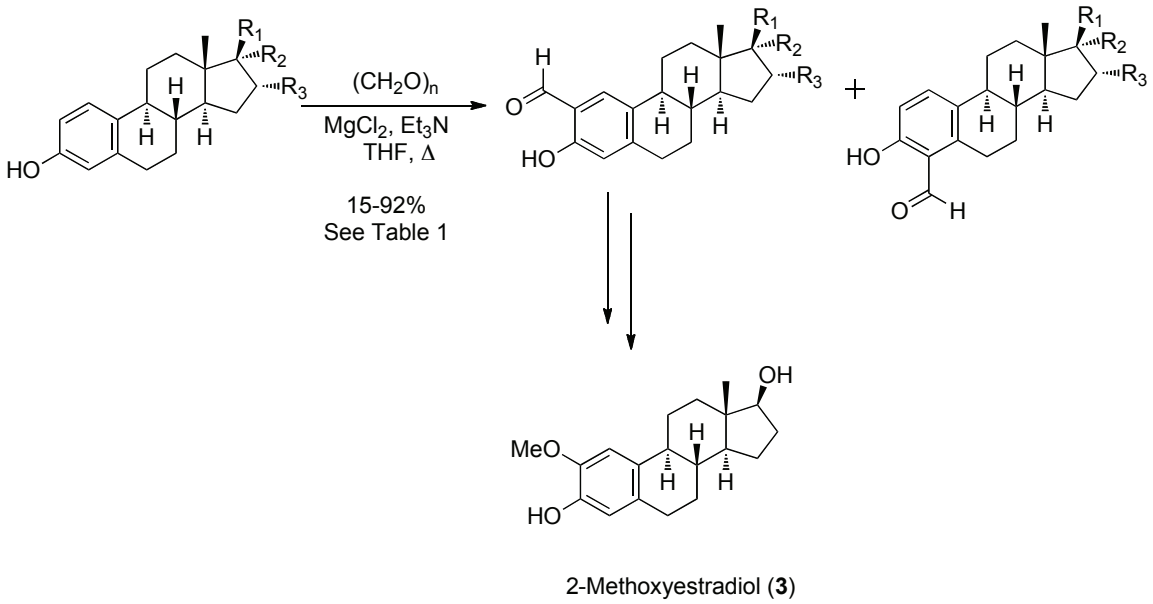

Figure 2. *ortho*-Formylation of estrogens.

Aromatic substituents have no detrimental effect on the reaction. Phenyl-,[10] perfluorophenyl-[11] and 2-nitrophenyl-substituted[11] phenols were formylated in good yields, and the same was the case with mono-protected 2,2´-bisphenol.[12] Naphthol derivatives behave similarly giving *ortho*-formylation products,[13,14] and of special merit is the preparation of 3-formyloctahydro-1,1´-binaphthol.[14b] 5-Methoxy-2-naphthol was formylated in 75% yield as part of the total synthesis of racemic juglomycin A.[15]

Oxygen functions are well tolerated; several mono protected resorcinols and methylenedioxy-substituted phenols have been formylated in excellent yields and high regioselectivity.[16,17] Moreover, several methylthio- and phenylthiophenol derivatives have been formylated in high yields.[18] Halogen-substituted phenols are good substrates in the reaction,[4] and this has been thoroughly substantiated in the last decade.[19]

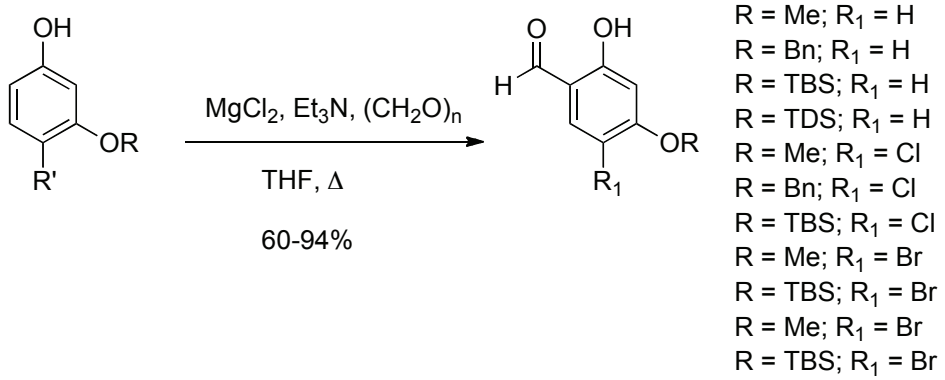

Figure 3. *Ortho*-formylation of mono-protected resorcinols.

The method also tolerates electron attracting groups like cyano and ester, but the reaction proceeds at a slower rate when these groups are attached to the benzene ring, and more byproducts may appear as well.[4] As anticipated, faster reactions were encountered when the ester group was further removed from the benzene ring. Formylation of **4** gave **5** in 94% yield[20] and reaction of the phenol **6** furnished aldehyde **7** in high yield (Figure 4).[21] The presence of two ester groups was accepted; formylation of dimethyl 2-(4-hydroxyphenyl)succinate proceeded with excellent yield.[22] Moreover, protected tyrosine, *viz*. methyl *N*-Cbz-tyrosinate was successfully formylated in 43% yield.[23] Since the formylation of 4-cyanophenol was successful,[4,24] it is interesting to note that (4-hydroxyphenyl)acetonitrile could not be formylated by the different methods tried.[25]

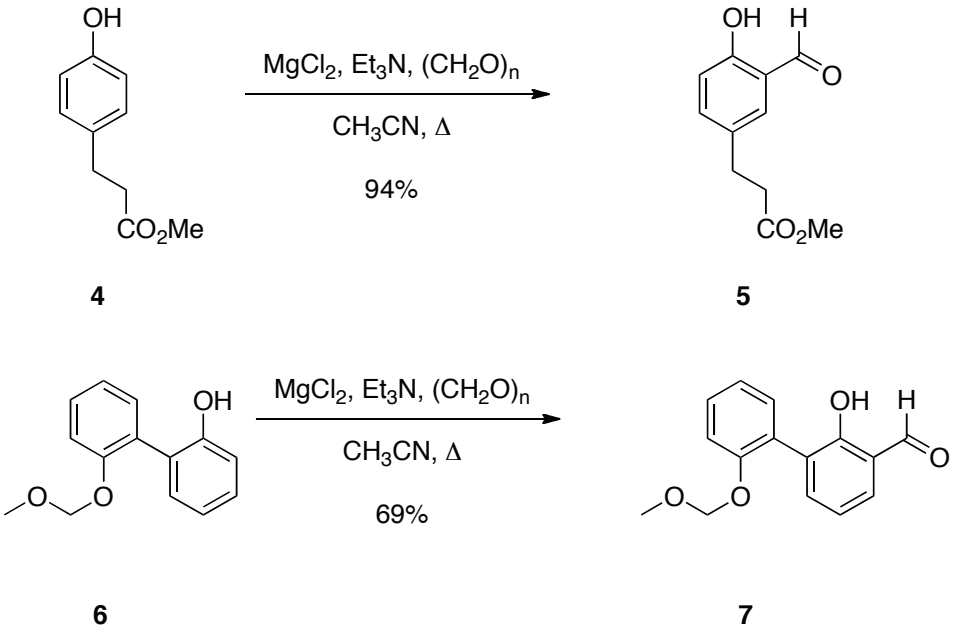

Figure 4. Examples of *ortho*-formylations.

The Formylation Method as Part of One-pot Reactions

Much can be gained with respect to efficiency and yields by using multi-component one-pot reactions, since several reactions can be carried out successively without isolation of intermediates. The reagents of this method appeared compatible for such a set-up, and several applications have been reported.

The catechol structural entity is present in natural products, many of biological interest. A one-pot preparation of catechols from the corresponding phenols has been reported[26] involving the formylation

reaction followed by Dakin or Baeyer-Villliger oxidations. The yields are very good (Figure 5). The method has been used in the synthesis of combretastatins A-1 and B-1.[27]

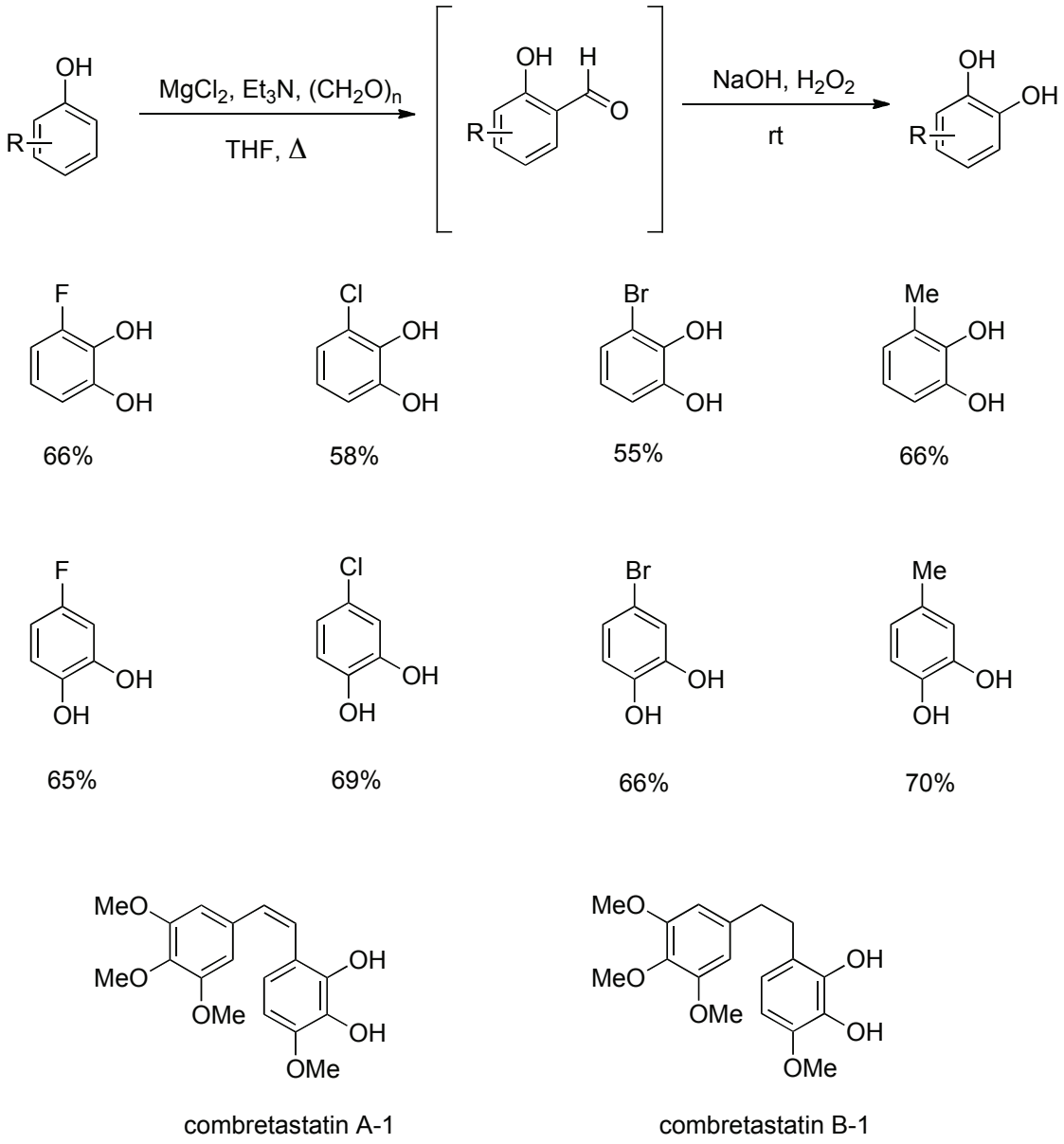

Figure 5. One-pot synthesis of catechols.

Salen ligands, that form part of the Jacobsen catalyst, were prepared in excellent yields by a one–pot reaction starting from the appropriate phenol (Figure 6).[28] The yields are considerably better than those previously obtained by a two-step protocol.

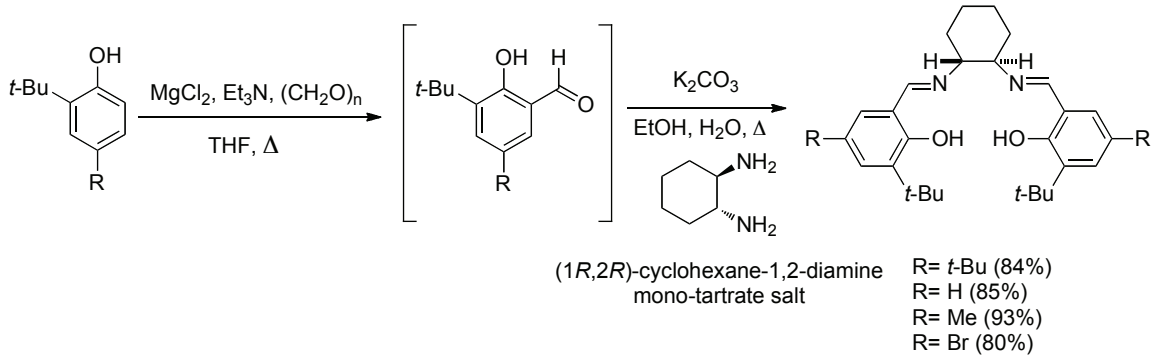

Figure 6. One-pot synthesis of salens.

By another one-pot reaction, salicylamines were prepared in good yields by reductive amination of the corresponding salicylaldehydes as outlined in Figure 7. The amines were further manipulated without isolation of intermediates to dihydro-2*H*-1,3-benzoxazines in good overall yields, considering the four reactions involved.[29] In a related one-pot procedure salicylnitriles were prepared.[30] In this case the imines formed from the respective salicylaldehyde and ammonia were oxidized with *o*-iodoxybenzoic acid to give good yields of the corresponding nitriles.

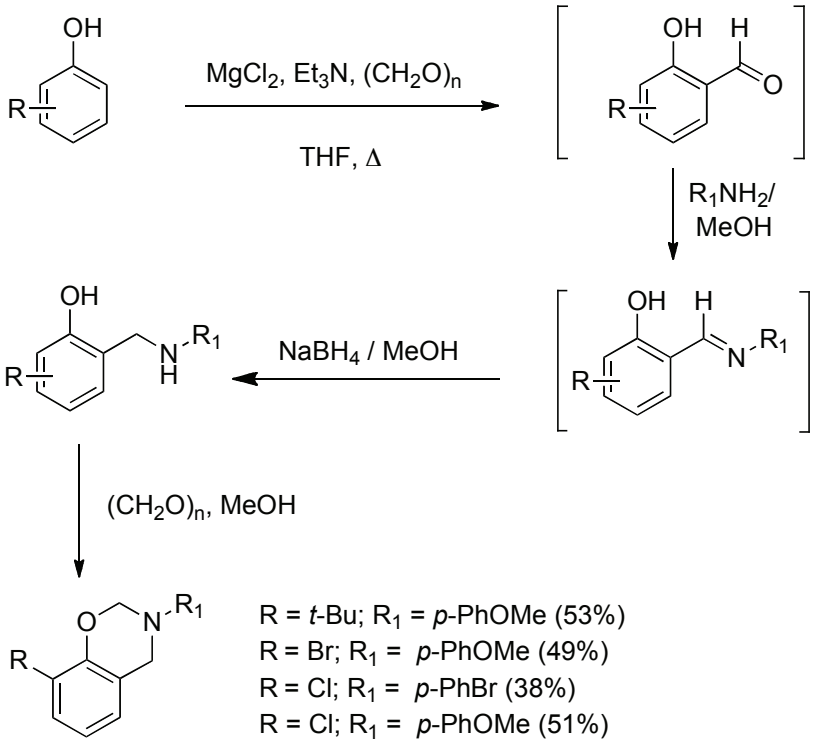

Figure 7. One-pot synthesis of salicylamines and dihydro-2*H*-1,3-benzoxazines.

Cinnamic acid derivatives are useful for the synthesis of heterocyclic compounds. Converting phenols to salicylaldehydes and subsequent treatment with methyl (triphenylphosporanylidene)acetate in a one-pot reaction afforded methyl 2-hydroxycinnamate derivatives in acceptable yields (Figure 8).[31]

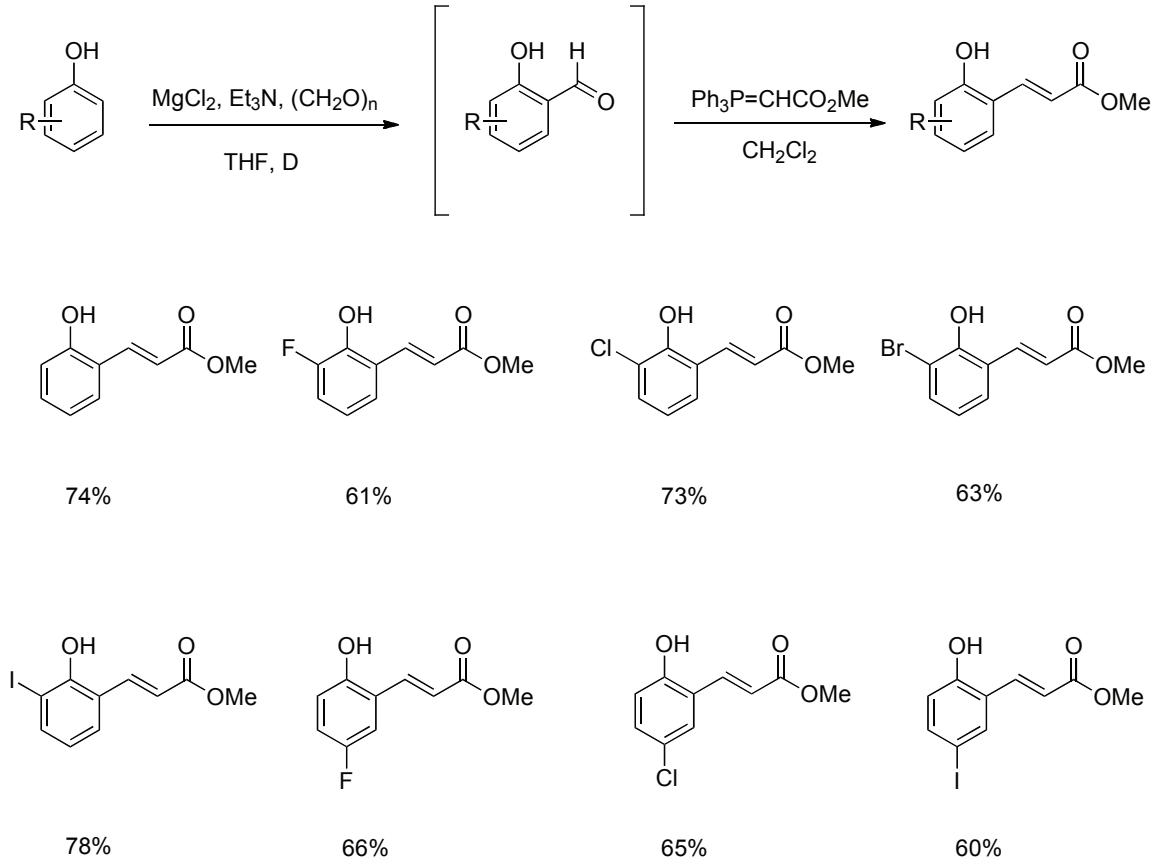

Figure 8. One-pot synthesis of methyl cinnamates.

Conclusion

The results have demonstrated that the method described above fits well into the assembly of phenol formylation reactions. It may prove to be the method of choice in many cases because of the ease of execution, regioselectivity, and good yields.

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