SYNLETT
Spotlight 47

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

The *N*-Cumyl Group for Facile Manipulation of Carboxamides, Sulfonamides and Aryl *O*-Carbamates Post-Directed *ortho* Metalation

Compiled by Costa Metallinos

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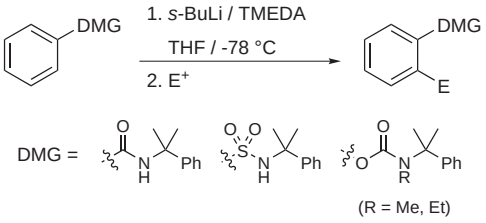
Directed metalation groups (DMGs) are sometimes compromised by the inability to convert them to different functionalities under mild conditions in post-directed *ortho* metalation (D*o*M) steps.[1] The advent of *N*-cumyl modified carboxamide, sulfonamide and *O*-carbamate DMGs,[2] whose primary advantages over analogous *N*-*t*-Bu[3] and other *N*-alkyl systems rest in fast and/or mild hydrolysis post-D*o*M, has opened new possibilities for the manipulation of substituted aromatics (Scheme 1). Starting materials are easily prepared by treating the appropriate benzoyl or sulfonyl chlorides with cumyl amine[4] for access to benzamides and sulfonamides, respectively, or by treating phenyl chloroformate with a secondary *N*-alkyl-*N*-cumyl amine[5] for *O*-carbamates.

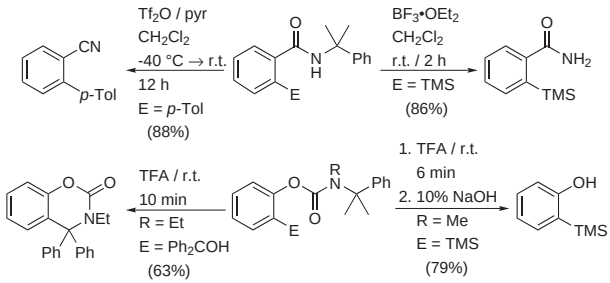
This Spotlight reviews several applications of *N*-cumyl-substituted functional groups in organic synthesis since the preliminary results of 1999.[2]



Scheme 1

Abstracts

ortho-Substituted *N*-cumylbenzamides and aryl *O*-carbamates may be easily decumylated[3] under a number of conditions.[2] Treatment of secondary *N*-cumylbenzamides with a Lewis acid ($BF_3{\cdot}OEt_2/CH_2Cl_2$/r.t.) gives primary amides in good yields, while application of Charette's conditions[6] (Tf_2O/pyridine/CH_2Cl_2/–40 °C) affords benzonitriles in one pot. Similarly, *O*-carbamates undergo rapid decumylation (TFA/r.t./6–10 min) to yield benzoxazines or secondary carbamates; the latter may be easily hydrolyzed to phenols (10% NaOH/EtOH/r.t.).



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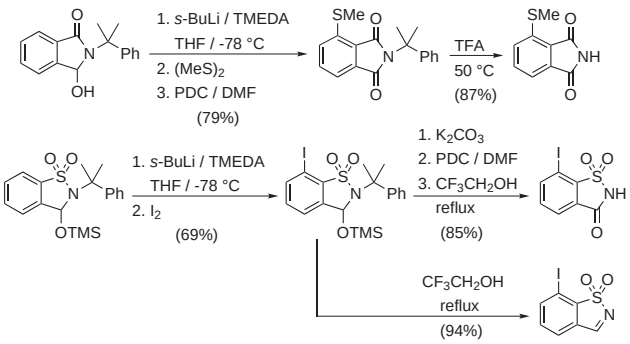
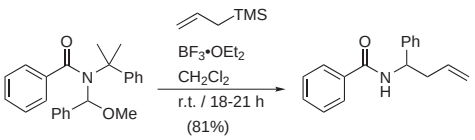
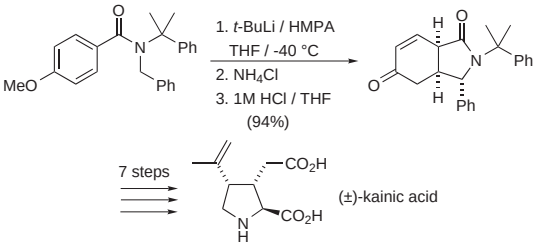
Metalation of *N*-cumyl phthalimidine (2.2 equiv *s*-BuLi/TMEDA/THF/–78 °C) followed by electrophile quench gives, after oxidation (PDC/DMF/r.t.) access to 3-substituted phthalimides that can be decumylated (TFA/50 °C/9–16 h) in high yield.[2] The method has been extended to TMS-protected sultams derived from *N*-cumylbenzenesulfonamide, to afford 7-substituted saccharins after simple desilylation (K_2CO_3/MeOH), oxidation (PDC/DMF/r.t.) and decumylation (CF_3CH_2OH/reflux/90 min).[7] Alternatively, decumylation of 7-substituted TMS-protected sultams (CF_3CH_2OH/reflux) provide direct access to 7-substituted benzisothiazole-1,1-dioxides.



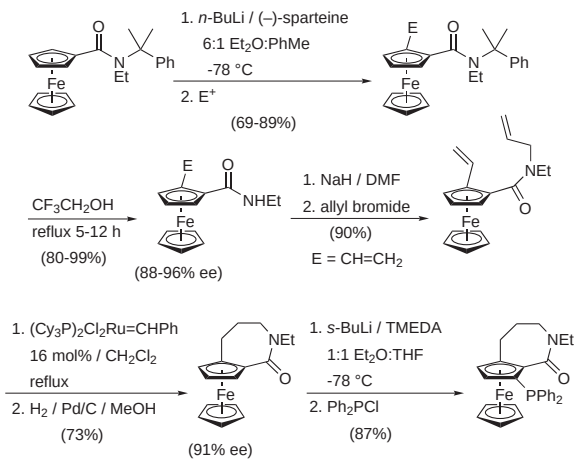
Weinreb has shown that *N*-cumyl-*N*-(α-methoxy)benzylbenzamides may be used to generate *N*-acylimines ($BF_3{\cdot}OEt_2$/CH_2Cl_2/r.t./18–21 h) which can be trapped with allyltrimethylsilane, with concomitant loss of the *N*-cumyl group, to afford *N*-homoallylic secondary benzamides.[8]



Clayden has used *N*-cumyl-*N*-benzylbenzamides to induce dearomatizing cyclization reactions,[9] initiated by benzylic anion formation (2 equiv *t*-BuLi/12 equiv HMPA/THF/–40 °C), to provide enone products after acidic workup. The use of cumyl as the *N*-protecting group in such systems was a key aspect to the successful synthesis of (±)-kainic acid,[10] since the corresponding *t*-Bu[3] analogue failed to dealkylate under identical conditions (TFA/reflux/6 h).



Enantioselective applications are also possible. *N*-Cumyl-*N*-ethylferrocenecarboxamide sterically mimics[11] *N*,*N*-diisopropylferrocenecarboxamide in (–)-sparteine-mediated metalation to provide 2-substituted ferrocenes in good yield. Unlike the original *N*,*N*-diisopropyl systems,[12,13] the products are open to flexible manipulation by virtue of decumylation under very mild conditions (CF_3CH_2OH/reflux/5–12 h)[3] to give, usually quantitatively, enantiomerically enriched secondary ferrocenecarboxamides for further transformations.[14] For example, *N*-allylation of *N*-ethyl-2-vinylferrocenecarboxamide followed by olefin metathesis with Grubbs' catalyst gives, after hydrogenation, a planar chiral ferrocenyl azepinone. Subsequent metalation and electrophile quench (Ph_2PCl) affords structurally novel phosphine ligands.[11]



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(2) Metallinos, C.; Nerdinger, S.; Snieckus, V. *Org. Lett.* **1999**, *1*, 1183.

(3) More forcing conditions are required to dealkylate *N*-*t*-Bu benzamides; see: Reitz, D. B.; Massey, S. M. *J. Org. Chem.* **1990**, *55*, 1375.

(4) (a) Cumyl amine can be prepared from cumyl alcohol by a modification of the procedure of: Balderman, D.; Kalir, A. *Synthesis* **1978**, 24. The azide is reduced with $LiAlH_4$ (Et_2O/0 °C → r.t. → reflux) or H_2 (Lindlar's catalyst/EtOH) instead of Raney nickel. (b) Cumyl amine is also commercially available from TCI America: catalogue no. C1293.

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