

# 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

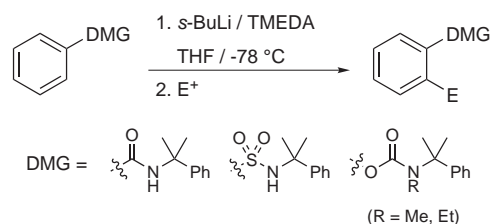
Costa Metallinos was born in Toronto, ON, Canada. He received a BSc degree from the University of Western Ontario and then pursued doctoral studies, first at the University of Waterloo, and then at Queen's University, under the supervision of Professor Victor Snieckus in the areas of synthetic methodology and asymmetric lithiation. He completed his PhD degree on September 11, 2001 and is currently a postdoctoral associate at Boston College with Professor T. Ross Kelly.

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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 (DoM) steps.<sup>1</sup> The advent of *N*-cumyl modified carboxamide, sulfonamide and *O*-carbamate DMGs,<sup>2</sup> whose primary advantages over analogous *N*-*t*-Bu<sup>3</sup> and other *N*-alkyl systems rest in fast and/or mild hydrolysis post-DoM, 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<sup>4</sup> for access to benzamides and sulfonamides, respectively, or by treating phenyl chloroformate with a secondary *N*-alkyl-*N*-cumyl amine<sup>5</sup> for *O*-carbamates.

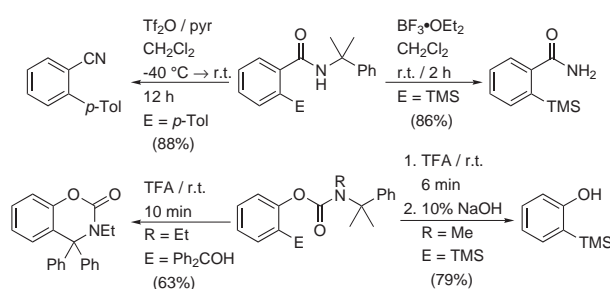
This Spotlight reviews several applications of *N*-cumyl-substituted functional groups in organic synthesis since the preliminary results of 1999.<sup>2</sup>



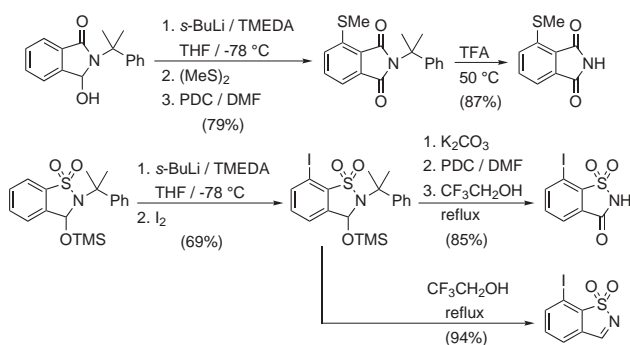
Scheme 1

### Abstracts

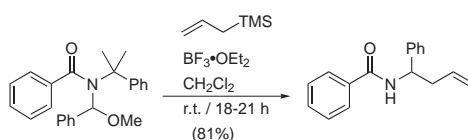
*ortho*-Substituted *N*-cumylbenzamides and aryl *O*-carbamates may be easily decumylated<sup>3</sup> under a number of conditions.<sup>2</sup> Treatment of secondary *N*-cumylbenzamides with a Lewis acid ( $\text{BF}_3 \cdot \text{OEt}_2 / \text{CH}_2\text{Cl}_2 / \text{r.t.}$ ) gives primary amides in good yields, while application of Charette's conditions<sup>6</sup> ( $\text{Tf}_2\text{O} / \text{pyridine} / \text{CH}_2\text{Cl}_2 / -40^\circ\text{C}$ ) affords benzonitriles in one pot. Similarly, *O*-carbamates undergo rapid decumylation ( $\text{TFA} / \text{r.t.} / 6\text{--}10\text{ min}$ ) to yield benzoxazines or secondary carbamates; the latter may be easily hydrolyzed to phenols ( $10\% \text{ NaOH} / \text{EtOH} / \text{r.t.}$ ).



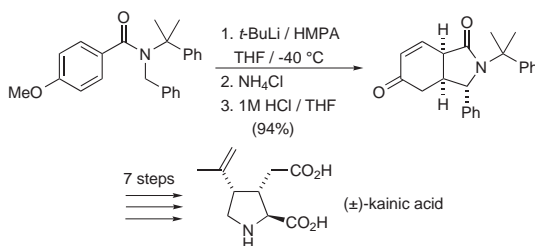
Metalation of *N*-cumyl phthalimidine (2.2 equiv *s*-BuLi/TMEDA/THF/−78 °C) followed by electrophile quench gives, after oxidation (PDC/DMF/r.t.) access to 3-substituted phthalimides that can be decumylated (TFA/50 °C/9–16 h) in high yield.<sup>2</sup> The method has been extended to TMS-protected sultams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



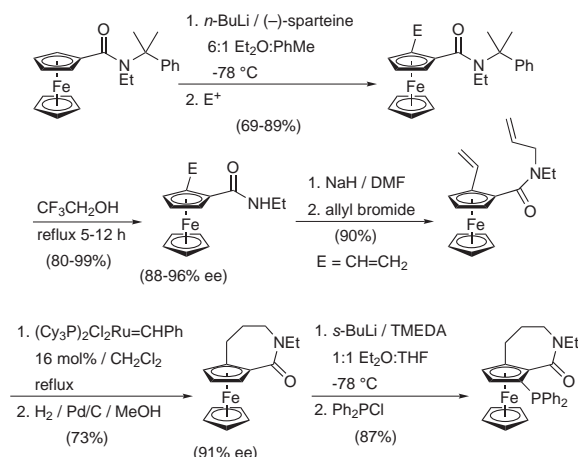
Weinreb has shown that *N*-cumyl-*N*-( $\alpha$ -methoxy)benzylbenzamides may be used to generate *N*-acylimines (BF<sub>3</sub>·OEt<sub>2</sub>/CH<sub>2</sub>Cl<sub>2</sub>/r.t./18–21 h) which can be trapped with allyltrimethylsilane, with concomitant loss of the *N*-cumyl group, to afford *N*-homoallylic secondary benzamides.<sup>8</sup>



Clayden has used *N*-cumyl-*N*-benzylbenzamides to induce de-aromatizing cyclization reactions,<sup>9</sup> 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 ( $\pm$ )-kainic acid,<sup>10</sup> since the corresponding *t*-Bu<sup>3</sup> analogue failed to dealkylate under identical conditions (TFA/reflux/6 h).



Enantioselective applications are also possible. *N*-Cumyl-*N*-ethylferrocenecarboxamide sterically mimics<sup>11</sup> *N,N*-diisopropylferrocenecarboxamide in (−)-sparteine-mediated metalation to provide 2-substituted ferrocenes in good yield. Unlike the original *N,N*-diisopropyl systems,<sup>12,13</sup> the products are open to flexible manipulation by virtue of decumylation under very mild conditions (CF<sub>3</sub>CH<sub>2</sub>OH/reflux/5–12 h)<sup>3</sup> to give, usually quantitatively, enantiomerically enriched secondary ferrocenecarboxamides for further transformations.<sup>14</sup> 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<sub>2</sub>PCl) affords structurally novel phosphine ligands.<sup>11</sup>



## References

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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<sub>4</sub> (Et<sub>2</sub>O/0 °C → r.t. → reflux) or H<sub>2</sub> (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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