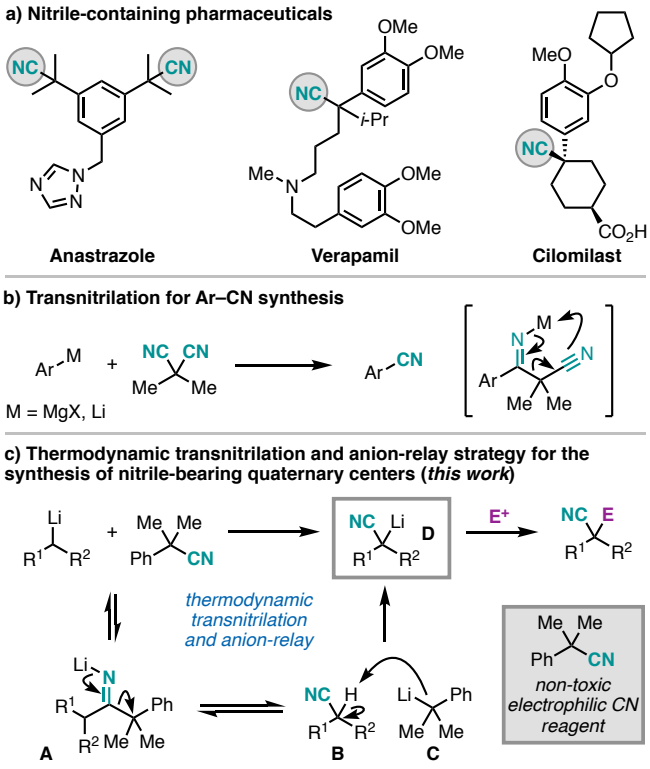
Synthesis of nitrile-bearing quaternary centers via an equilibrium-driven transnitrilation and anion-relay strategy

Sébastien Alazet,[a] Michael S. West,[a] Purvish Patel,[a] and Sophie A. L. Rousseaux*[a]

Abstract: The efficient preparation of nitrile-containing building blocks is of interest due to their utility as synthetic intermediates and their prevalence in pharmaceuticals. As a result, significant efforts have been made to develop methods to access these motifs which rely on safer and non-toxic sources of CN. Herein, we report that 2-methyl-2-phenylpropanenitrile is an efficient, non-toxic, electrophilic CN source for the synthesis of nitrile-bearing quaternary centers via a thermodynamic transnitrilation and anion-relay strategy. This one-pot process leads to nitrile products resulting from the *gem*-difunctionalization of alkyl lithium reagents.

The rapid generation of molecular complexity is a long-standing objective in organic chemistry.[1] One-pot transformations, which avoid the purification of synthetic intermediates, not only accelerate the synthesis of complex molecules but also minimize the amount of waste generated in the process. Complex nitrile-containing molecules are of interest to the community due to their versatility as synthetic intermediates for the generation of amines, ketones, carboxylic acids and aldehydes.[2] They are also found in numerous pharmaceuticals (Scheme 1a).[3] As a result, a wide variety of methods for the preparation of nitrile-containing building blocks have been developed with recent efforts focusing on the use of safer and non-toxic sources of CN.[4] Of particular interest are reactions that avoid the use or generation of cyanide ions.[5] Herein, we report a method for the generation of all-carbon quaternary centers bearing a nitrile group from secondary alkyl lithiums (or halides) using a one-pot transnitrilation, anion-relay[6] and electrophile-trapping strategy (Scheme 1c). This method uses 2-methyl-2-phenylpropanenitrile as a non-toxic electrophilic CN source, avoiding the use of cyanide salts that are typically involved in the synthesis of alkylnitriles from alkyl halides.

We were inspired by a recent report by Reeves and co-workers who have demonstrated that dimethylmalononitrile is an efficient, non-toxic, carbon-bound electrophilic CN source for the transnitrilation of aryl Grignard reagents and aryllithiums (Scheme 1b).[5a, b] The reaction is proposed to occur via addition of the organometallic reagent to a nitrile group and retro-Thorpe fragmentation to yield the corresponding aryl nitriles. Given our interest in the synthesis of nitrile-containing molecules,[7] we wondered if a similar strategy could be applied for the *gem*-difunctionalization of alkyl lithium reagents via an equilibrium-driven transnitrilation and anion-relay process (Scheme 1c). Addition of the organometallic reagent to an appropriately functionalized electrophilic CN source would yield lithium imine **A**, which fragments to generate nitrile intermediate **B** along with tertiary organolithium intermediate **C**.[8] It should be noted that this transnitrilation process is under thermodynamic control (i.e. reversible) and that tuning the basicity of the leaving group in the electrophilic CN source is crucial for pushing the equilibrium towards transnitrilated organolithium intermediate **D**, which can be trapped with an electrophile to generate the *gem*-difunctionalized product. With a more reactive transnitrilation reagent such as dimethylmalononitrile,[5b] the leaving group is not basic enough for complete conversion to **D**, and subsequent electrophile-trapping leads to mixtures of products.



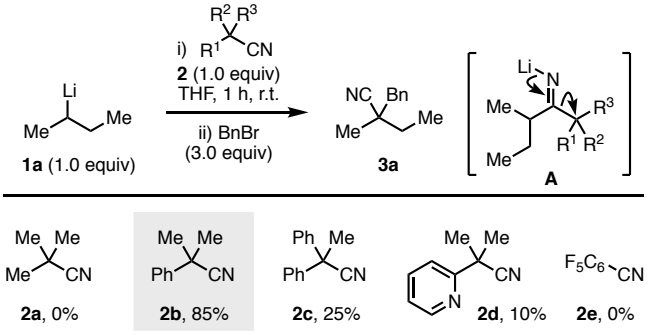
Scheme 1. Transnitrilation strategies for the synthesis of pharmaceutically-relevant nitrile-containing building blocks.

We initiated our study by evaluating the transnitrilation of *s*-BuLi (**1a**) with various electrophilic nitrile sources (**2**). Benzyl bromide was chosen as a terminal electrophile to trap the anion resulting from fragmentation of the lithium imine intermediate (Scheme 2). We began by examining a range of nitrile sources (**2a**-**2e**) with varying electronic properties. Trimethylacetonitrile **2a** is not an efficient transnitrilation reagent since none of the desired product **3a** was observed in this transformation. Only the imine, resulting from addition of **1a** to **2a**, was obtained. We hypothesized that fragmentation of the lithium imine **A** to release *t*-BuLi was too challenging and that a transnitrilation reagent containing a better leaving group would be more efficient for this transformation. While dimethylmalononitrile would be efficient for the transnitrilation process, as reported by Reeves and

[a] Dr. S. Alazet, M. S. West, P. Patel. Prof. Dr. S. A. L. Rousseaux
Davenport Research Laboratories, Department of Chemistry
University of Toronto
80 St George Street, Toronto, Ontario, M5S 3H6 (Canada)
E-mail: sophie.rousseaux@utoronto.ca

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

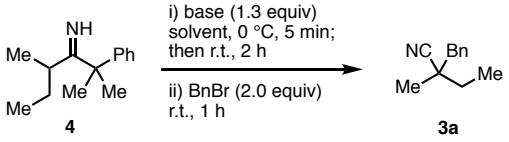
coworkers,[5b] the anion resulting from the retro-Thorpe fragmentation would not be basic enough to drive the anion-relay process. With these considerations in mind, we examined the use of benzylic nitrile **2b** as an electrophilic CN source in our reaction. Product **3a** was obtained in 85% from **2b** after a brief optimization of the reaction conditions, which revealed that addition of *s*-BuLi to the electrophilic nitrile source and subsequent fragmentation of the lithium imine intermediate (**A**) was efficient in THF at room temperature in 1 hour. Transnitrilation reagents **2c** and **2d** afforded the desired product but in low yields. In both cases, formation of the lithium imine (**A**) was efficient, however fragmentation of this intermediate was inefficient for **2d** while anion-relay and alkylation by benzyl bromide was low yielding for the reaction using **2c**. This demonstrates the need to subtly tune the electronic properties of the transnitrilation reagent to observe the desired thermodynamic *gem*-difunctionalized product. Finally, the reaction of **1a** with **2e** led to a complex mixture of products, possibly due to the poor stability of the highly electron-deficient lithium imine intermediate. It is interesting to note that Grignard reagents did not react with **2b** at room temperature. High temperatures (refluxing in THF) were required for metal imine formation, but the product resulting from the nitrile transfer process was not obtained.



Scheme 2. Evaluation of electrophilic CN sources. Yields determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

To better understand the conditions required for fragmentation of the metal imine intermediate, imine **4** was treated with various bases and subsequently treated with benzyl bromide to yield **3a** (Table 1). *n*-BuLi, NaHMDS and KHMDS (entries 1-3) efficiently enabled the formation of **3a** in 69%, 65% and 75% yield, respectively, using THF as the solvent mixture. Treating imine **4** with Et_2Zn or MeMgBr did not result in fragmentation, and **4** was recovered (entries 4-5). Other ethereal solvents were also examined in the fragmentation of **4** with *n*-BuLi since the alkyllithium reagents that will be used for this transnitrilation and anion-relay process are generally prepared in Et_2O or in Et_2O/hydrocarbon solvent mixtures.[9] The imine fragmentation process appears to be highly solvent-dependent. Product **3a** was not observed in reactions performed in Et_2O or 1,4-dioxane, as well as in other ethereal solvents (entries 6-7 and Table S1). Thus, a solvent switch to THF may be necessary when exploring the reaction scope with respect to various alkyllithium reagents (see Scheme 4).

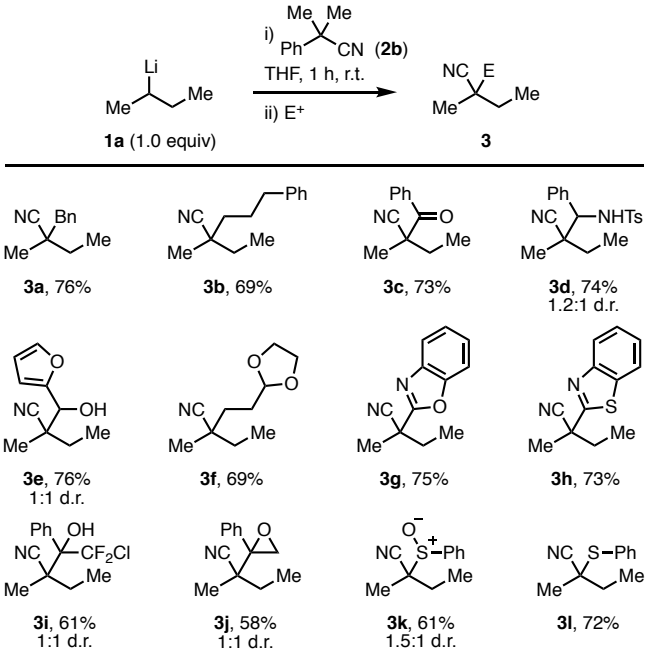
Table 1. Optimization of the reaction conditions for imine fragmentation.



Entry	Base	Solvent	Yield (%)[a]
1	*n*-BuLi	THF	69
2	NaHMDS	THF	65
3	KHMDS	THF	75
4	Et_2Zn	THF	0
5	MeMgBr	THF	0
6	*n*-BuLi	Et_2O	0
7	*n*-BuLi	Dioxane	0

[a] Determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

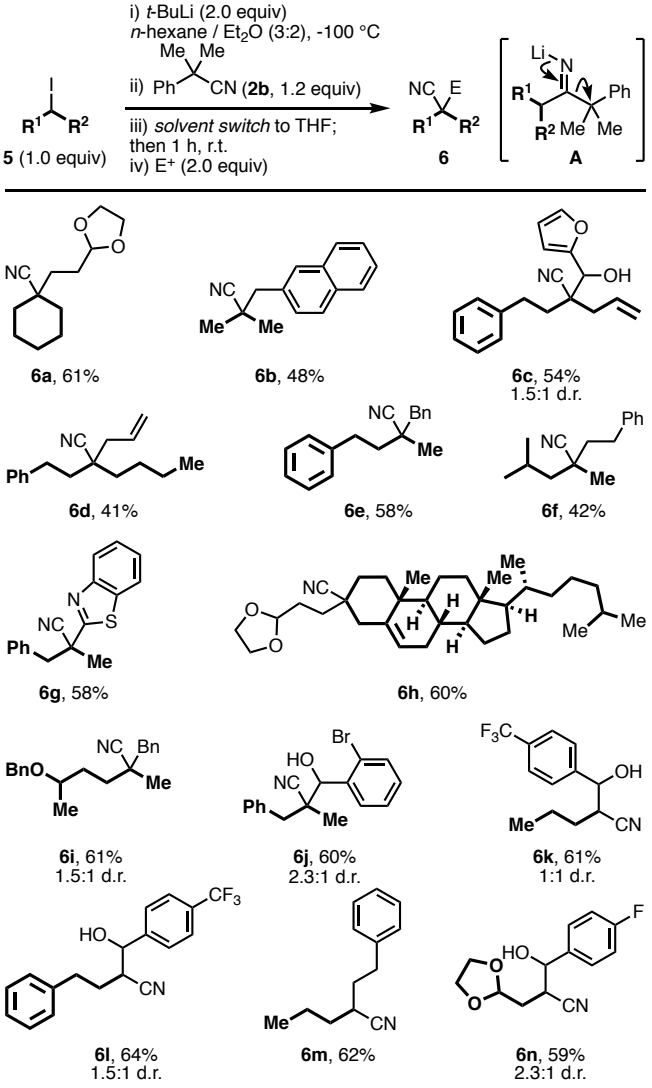
Having determined that **2b** is an optimal reagent for transnitrilation and anion-relay functionalization of alkyllithiums, we next explored the scope of electrophiles that can be used in this transformation.[10] A commercially available solution of *s*-BuLi (1.4 M in cyclohexane) was used as the model substrate (Scheme 3). Alkyl halides were efficient electrophiles in this transformation, affording products **3a**, **3b** and **3f** in good yields. Carbonyl-based electrophiles, such as benzoyl chloride, *N*-tosyl imine, an aldehyde and a ketone, provided *gem*-difunctionalized products **3c, 3d**, **3e** and **3i**, respectively, in good yields. Tertiary epoxide **3j** was obtained in a 58% yield using 2-bromoacetophenone as the electrophile. Products **3g** and **3h** were obtained via nucleophilic aromatic substitution of the corresponding 2-chlorobenzoxazole and 2-chlorobenzothioazole in 75% and 73% yield, respectively. Finally, trapping the transnitrilated organolithium intermediate with methyl benzenesulfinate or phenyl disulfide yielded products **3k** and **3l** in 61% and 72%, respectively.



Scheme 3. Reaction scope for the tandem transnitrilation and electrophilic *gem*-difunctionalization of *s*-BuLi. Reported yields are isolated yields for an average of two reactions. See the Supporting Information for experimental details.

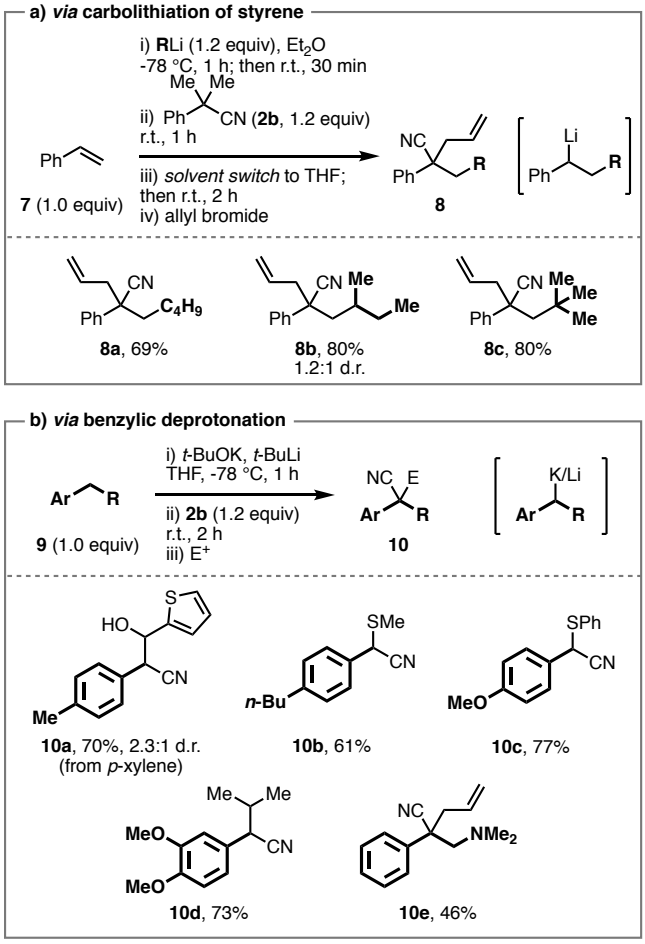
The scope of this reaction with respect to the alkyllithium reagent is shown in Scheme 4. Starting from alkyl iodides, various substituted organolithium reagents were prepared via lithium-halogen exchange.[9] Using Knochel's procedure,[11] alkyllithiums were prepared *in situ* and trapped with the electrophilic CN source **2b**. Since the alkyllithium reagents in these reactions are generated in a mixture of Et_2O and *n*-hexane, the resulting lithium imines **A** do not fragment to initiate the anion-relay process. Removing the solvent and dissolving **A** in THF leads to fragmentation and deprotonation to generate the transnitrilated organolithium intermediates (**D** in Scheme 1), which can be trapped with various electrophiles. Various secondary alkyl iodides were successfully converted to the corresponding functionalized nitrile derivatives **6a**-**6j** in moderate to good yields (Scheme 4). Various electrophiles, including aldehydes (**6c**, **6j**) and 2-chlorobenzothioazole (**6g**), were also used in these reactions, generating diverse products. Functional groups including an acetal (**6a**, **6h**), allyl (**6c**, **6d**), benzyl-protected alcohol (**6i**) and aryl bromide (**6j**) provide handles for further product diversification.

Overall, these reactions lead to the formation of two new C–C bonds and the generation of an all-carbon quaternary center bearing a nitrile functional group. This 4-step, one-pot sequence occurs in good yields from readily available secondary alkyl halide starting materials. Most notably, in comparison with traditional synthetic sequences involving the nucleophilic cyanation of alkyl halides, this transformation avoids the use of hazardous cyanide anions and is not plagued by elimination side-reactions as is often observed with secondary alkyl halides.[12, 13] Using our transnitrilation and anion relay strategy, the direct cyanation and functionalization of iodocyclohexyl derivatives was achieved with good yields. Simple cyclic building block **6a** or natural product analogue **6h** were obtained in this one-pot protocol in 61% and 60% yield, respectively. The formation of products **6c** and **6d** was more challenging due to low conversion of the alkyl iodide to the corresponding organolithium during the first step of the reaction. Side-products resulting from elimination and reduction reactions were also observed.[11, 14] A slight excess of iodoalkane (2.0 equiv) and *t*-BuLi relative to **2b** was required to obtain products **6c** and **6d** in 54% and 41%, respectively.



Scheme 4. Reaction scope for the tandem transnitrilation and electrophilic *gem*-difunctionalization of alkyllithium reagents. Reported yields are isolated yields for an average of two reactions. See the Supporting Information for experimental details.

The synthesis of nitrile-bearing tertiary centers was achieved using primary alkyl lithium reagents (Scheme 4, **6k**-**6n**). Using *n*-BuLi (**6k**), we found that the fragmentation of imine **A** (where R^1 = C_3H_7 and R^2 = H) required higher dilution in THF (0.25 M) and a longer time reaction (2 h).[15] Primary alkyl iodides also participated in the one-pot lithium-halogen exchange, transnitrilation, anion-relay and electrophile trapping reaction. Nitriles **6l**-**6n** were obtained in good yields using this sequence.



Scheme 5. Synthesis of α-arylnitriles via a) carbolithiation of styrene and b) selective deprotonation of toluene derivatives. Reported yields are isolated yields for an average of two reactions. See the Supporting Information for experimental details.

Diverse α-arylnitriles, which are not only versatile synthetic intermediates but are also prevalent in pharmaceuticals,[3] could be prepared using our transnitrilation strategy (Scheme 5). Two strategies for the generation of benzylithium reagents were investigated: carbolithiation of styrene (Scheme 5a)[16] and selective deprotonation of toluene derivatives (Scheme 5b).[17] Using the carbolithiation protocol, three new C–C bonds can be formed in a one-pot process to generate functionalized α-arylnitriles from styrene and **2b** as the electrophilic CN source. As a proof of concept, products **8a**-**8c** were prepared in 69-80% using *n*-BuLi, *s*-BuLi and *t*-BuLi as nucleophiles. A solvent switch to THF was required here too to initiate fragmentation of the lithium imine intermediate.

Selective benzylic deprotonation using a superbase, generated by the addition of *t*-BuOK to an alkyllithium (*n*-BuLi or *t*-BuLi),[17a] was also explored as a means to access α-arylnitriles from toluene derivatives (Scheme 5b). The addition of *t*-BuOK increases the basicity of the organolithium species, which can efficiently deprotonate benzylic positions. We chose to use this metalation protocol for our one-pot transnitrilation and anion-relay reaction, as the deprotonation could take place in THF, which avoids a solvent switch step in the process. Using this strategy, α-arylnitriles **10a**-**10e** were prepared from very simple starting materials. For example, *p*-xylene was converted to product **10a** in 70% yield, and **10b** was obtained selectively from *p*-butyltoluene in 61% yield. Benzyl cyanide derivatives are generally obtained from the corresponding benzyl halides using nucleophilic cyanide salts. These benzyl halides are typically prepared from the corresponding toluene derivatives via radical halogenation, which can lead to regioselectivity challenges in more substituted derivatives. Using our method, complete selectivity for the transnitrilated products **10a** and **10b** is observed. Products resulting from dicyanation or regioisomers (in the case of **10b**) are not observed. For the synthesis of **10c** and **10d**, TMPH was used as an additive to generate a potassium/lithium amide. This helps to avoid the formation of side-products resulting from directed *ortho* metalation by the OMe group.[17b, d] Complete selectivity for deprotonation of the methyl group was observed and the corresponding secondary benzylic nitriles were synthesized in excellent yields. Product **10d** is an intermediate in the synthesis of verapamil, a drug on the WHO's List of Essential medicines (Scheme 1a). Finally, using a method reported by Strohmann and coworkers for the direct metalation of sensitive benzyl derivatives such as (2-phenylethyl)-dimethylamine,[17c] product **10e** was obtained in 46% yield. While the secondary benzyllithium intermediate in this reaction is known to undergo β-elimination reactions,[17c] this side reaction can be avoided by using a mixture of *t*-BuOK and *t*-BuLi in THF at -78 °C.

In summary, we have developed a one-pot method for the synthesis of various nitrile-containing building blocks based on an equilibrium driven transnitrilation and anion-relay strategy. A broad range of electrophiles and alkyl lithium reagents, generated via lithium-halogen exchange, carbolithiation or benzylic deprotonation, participate in this reaction. The nature of the transnitrilation reagent is crucial for the success of this one-pot *gem*-difunctionalization process; not only must it readily generate lithium imine adducts (**A**) under mild conditions, but it must also fragment to generate a base responsible for anion-relay. Other applications of transnitrilation strategies for the synthesis of nitrile-containing building blocks are currently being explored in our laboratory.

Acknowledgements

We thank NSERC (Discovery Grants and Canada Research Chairs programs), the Canada Foundation for Innovation (project number 35261), the Ontario Research Fund and the University of Toronto for generous financial support of this work.

Conflict of interest

The authors declare no conflict of interest.

Keywords: transnitrilation • anion-relay strategy • alkylnitriles • alkyl lithium reagents • fragmentation

[1] a) H. M. L. Davies, E. J. Sorensen, *Chem. Soc. Rev.* **2009**, *38*, 2981-2982; b) J. Li, M. D. Eastgate, *Org. Biomol. Chem.* **2015**, *13*, 7164-7176; c) T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**,

38, 3010-3021; d) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2011**, *50*, 6234-6246.

[2] a) R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Wiley, New York, **1989**; b) Z. Rappoport, *Chemistry of the Cyano Group*, Wiley, London, **1970**.

[3] F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.* **2010**, *53*, 7902-7917.

[4] *Science of Synthesis: Three Carbon-Heteroatom Bonds: Nitriles, Isocyanides, and Derivatives, Vol. 19* (Ed.: S. Murahashi), Georg Thieme, Stuttgart, **2004**.

[5] a) J. L. E. Erickson, M. M. Barnett, *J. Am. Chem. Soc.* **1935**, *57*, 560-562; b) J. T. Reeves, C. A. Malapit, F. G. Buono, K. P. Sidhu, M. A. Marsini, C. A. Sader, K. R. Fandrick, C. A. Busacca, C. H. Senanayake, *J. Am. Chem. Soc.* **2015**, *137*, 9481-9488; c) C. A. Malapit, I. K. Luvaga, J. T. Reeves, I. Volchkov, C. A. Busacca, A. R. Howell, C. H. Senanayake, *J. Org. Chem.* **2017**, *82*, 4993-4997; d) C. A. Malapit, J. T. Reeves, C. A. Busacca, A. R. Howell, C. H. Senanayake, *Angew. Chem. Int. Ed.* **2016**, *55*, 326-330; e) P. Yu, B. Morandi, *Angew. Chem. Int. Ed.* **2017**, *56*, 15693-15697; f) X. Fang, P. Yu, B. Morandi, *Science* **2016**, *351*, 832-836; g) X. Fang, P. Yu, G. Prina Cerai, B. Morandi, *Chem. Eur. J.* **2016**, *22*, 15629-15633; h) A. M. Nauth, T. Opatz, *Org. Biomol. Chem.* **2019**, *17*, 11-23; i) J. Schörgenhumer, M. Waser, *Org. Chem. Front.* **2016**, *3*, 1535-1540.

[6] a) A. B. Smith, W.-S. Kim, *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6787-6792; b) I. I. I. A. B. Smith, W. M. Wuest, *Chem. Commun.* **2008**, 5883-5895.

[7] N. W. M. Michel, A. D. M. Jeanneret, H. Kim, S. A. L. Rousseaux, *J. Org. Chem.* **2018**, *83*, 11860-11872.

[8] a) G. B. Gregory, A. L. Johnson, W. C. Ripka, *J. Org. Chem.* **1990**, *55*, 1479-1483; b) S. S. Kulp, A. Romanelli, *Org. Prep. Proced. Int.* **1992**, *24*, 7-12; c) J.-M. R. Mattalia, *Beilstein J. Org. Chem.* **2017**, *13*, 267-284.

[9] F. Leroux, M. Schlosser, E. Zohar, I. Marek, in *PATAI'S Chemistry of Functional Groups*, **2009**.

[10] a) D. Nath, F. F. Fleming, *Angew. Chem. Int. Ed.* **2011**, *50*, 11790-11793; b) D. Nath, F. F. Fleming, *Chem. Eur. J.* **2013**, *19*, 2023-2029; c) D. Nath, M. C. Skilbeck, I. Coldham, F. F. Fleming, *Org. Lett.* **2014**, *16*, 62-65; d) X. Yang, D. Nath, F. F. Fleming, *Org. Lett.* **2015**, *17*, 4906-4909; e) X. Yang, D. Nath, M. R. Gau, O. W. Steward, F. F. Fleming, *Angew. Chem. Int. Ed.* **2017**, *56*, 7257-7260.

[11] S. Seel, G. Dagousset, T. Thaler, A. Frischmuth, K. Karaghiosoff, H. Zipse, P. Knochel, *Chem. Eur. J.* **2013**, *19*, 4614-4622.

[12] a) R. Smiley, C. Arnold, *J. Org. Chem.* **1960**, *25*, 257-258; b) F. L. Cook, C. W. Bowers, C. L. Liotta, *J. Org. Chem.* **1974**, *39*, 3416-3418; c) J. E. Shaw, D. Y. Hsia, G. S. Parries, T. K. Sawyer, *J. Org. Chem.* **1978**, *43*, 1017-1018.

[13] For comparison, (3-iodobutyl)benzene was converted to (3-cyanobutyl)benzene in 50% yield via nucleophilic cyanation using NaCN. This nitrile product could be converted to **6e** via deprotonation/alkylation. The overall yield for the synthetic sequence is 45%. See the Supporting Information for details.

[14] E. C. Ashby, T. N. Pham, *J. Org. Chem.* **1987**, *52*, 1291-1300.

[15] See the Supporting Information for details.

[16] a) A. Gómez-SanJuan, N. Sotomayor, E. Lete, *Beilstein J. Org. Chem.* **2013**, *9*, 313-322; b) S. Norsikian, I. Marek, S. Klein, J. F. Poisson, J. F. Normant, *Chem. Eur. J.* **1999**, *5*, 2055-2068; c) X. Wei, P. Johnson, R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1109-1116; d) X. Wei, R. J. K. Taylor, *Chem. Commun.* **1996**, 187-188.

[17] a) M. Schlosser, in *Pure Appl. Chem., Vol. 60*, **1988**, p. 1627; b) P. Fleming, D. F. O'Shea, *J. Am. Chem. Soc.* **2011**, *133*, 1698-1701; c) C. Unkelbach, H. S. Rosenbaum, C. Strohmann, *Chem. Commun.* **2012**, *48*, 10612-10614; d) A. Manvar, P. Fleming, D. F. O'Shea, *J. Org. Chem.* **2015**, *80*, 8727-8738.