Development of a Highly Selective Synthesis of 4-Substituted Tetrahydroquinolines: Substrate Scope and Mechanistic Study

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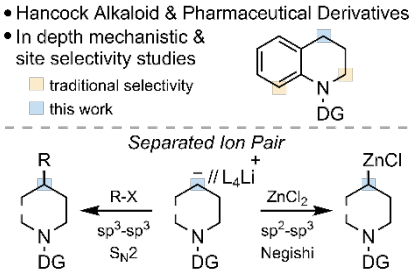
Abstract

Herein, we describe a general and selective deprotonation functionalization reaction of tetrahydroquinolines at the 4–position using organolithiums and phosphoramide ligands. In addition to the development of a direct deprotonation alkylation reaction with primary and secondary alkyl halides, a Negishi cross–coupling protocol was realized to afford products with a range of aromatic halides. These methods were applied to the late-stage installation of tetrahydroquinolines into a variety of substrates including pharmaceuticals as well as natural product analogues. The use of thorough mechanistic investigations revealed the aggregation state of the newly formed tetrahydroquinoline anion to be a separated ion pair, which proved critical to optimizing the reaction conditions.



1.0 INTRODUCTION

Tetrahydroquinolines (THQ) are privileged scaffolds that are commonly found in a variety of natural products[1] and small molecule therapeutics[2] (Figure 1A).[3] Given their medicinal properties numerous synthetic strategies have been established to construct and modify these heterocyclic cores.[4,5] While highly efficient ring building reactions may be accomplished to access THQ in many ways, they are time consuming and costly for researchers because most of the molecular complexity must be preinstalled prior to the cyclization event. On the other hand, the ability to modify the heterocyclic core directly opens a pathway to quickly access large libraries of structural derivatives.

Although the generality of C–H activation reactions has improved, many chemoselective bond forming processes can be performed without modifying the target compound, the majority of methods still rely on the presence of nearby reactive functional groups for high selectivities.[6] As a result, the development of methods to selectively functionalize heteroatoms far from the periphery of nitrogen remains a formidable synthetic challenge due to the difficulties in selecting a single C–H bond. For example, functionalization at the 4–position of THQ is traditionally pre–installed and the scaffold is cyclized through both electronic (Friedel–Crafts)[7] and directing effects (Lewis acid coordination)[8] (Figure 1B). In this regard, a straightforward approach to access 4–substituted tetrahydroquinolines would be to develop an undirected deprotonation capture sequence to the THQ framework.

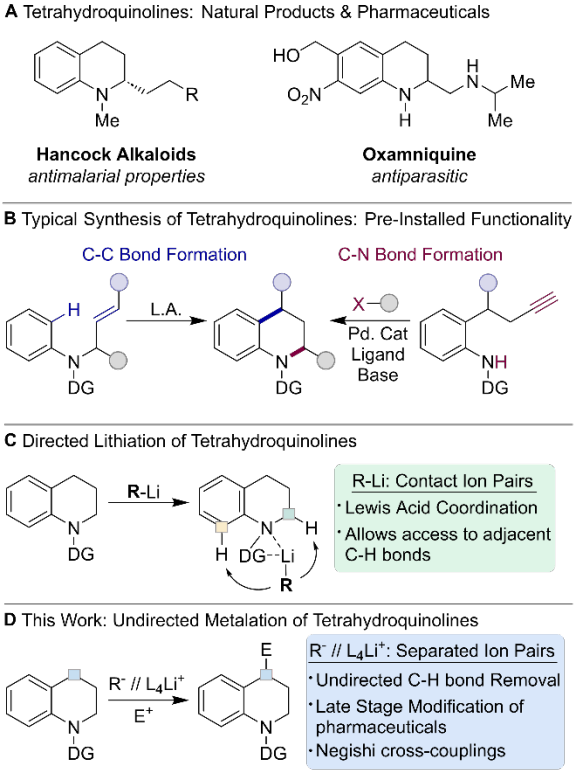


Figure 1. Overview of tetrahydroquinolines. A) Examples of natural products and pharmaceutical agents containing tetrahydroquinoline subunits. B) Current synthetic strategies to access tetrahydroquinolines bearing functionality at the 4–position. C) Traditional reactivity of contact ion pairs to undergo directed metalation. D) This work: functionalization of tetrahydroquinolines at the 4–position via an undirected deprotonation capture approach.

Given their widespread availability and continued success in both academia and industry, organolithium reagents are the ideal class of bases to effect such transformations. However, almost invariably, for controlled deprotonations to occur, the substrate must bear a heteroatom to coordinate the Li–atom which guides the deprotonation event to occur in proximity to the heteroatom – an inescapable consequence of the ability for the carbon–lithium bond to simultaneously serve as both a Lewis acid and Brønsted base (Figure 1C).[9] Therefore, the main challenges associated with such an undirected deprotonation strategy involves the design of reaction conditions that prevent the Li–atom from interacting with the substrate during the deprotonation event while maintaining high chemoselectivity for the desired C–H bond.

Last year, our laboratory demonstrated the feasibility of this approach, specifically by generating separated ion pairs (R^- // L_4Li^+) that bypass prototypical directed–*ortho* metalation pathways by disrupting the interactions between oxygen heterocycles with organolithium bases.[10] In this report we describe our continued exploration of this concept by investigating the site selective deprotonation of THQ incorporating various N–substitution patterns *via* highly basic separated ion pair intermediates (Figure 1D). Because the Li–atom valences are saturated (L_4Li^+) within the separated ion pair, various N–substitution patterns, such as N–Ph, N–Me, and N–Boc, could be bypassed allowing for a highly selective synthesis of 4–substituted tetrahydroquinolines. In addition, the development of direct alkylation reactions with primary and secondary alkyl halides, and a general Negishi cross–coupling protocol with various aromatic electrophiles were realized. Importantly, we have demonstrated that our protocol exhibits substantial functional group compatibilities through the preparation of natural product analogues and the late–stage modification of FDA approved pharmaceuticals.

2.0 RESULTS AND DISCUSSION

2.1. Site Selectivity of Metalation with Tetrahydroquinolines: Effect of Lewis Basic Additives. To determine a general method to functionalize the benzylic position within the THQ framework, several derivatives incorporating diverse N–substitution patterns were selected and examined in parallel. To ensure that our selectivity investigations were rigorous, common N–directing groups, such as *tert*–butyloxycarbonyl (Boc) which are known to enable effective directed–*ortho* deprotonation, were included in our site selectivity investigations. These substrates were selected to elucidate a lithiation method that overrides common directing effects over a wide range of THQ derivatives. A typical reaction sequence involved treating the THQ derivative in a 1:1 ratio with an organolithium reagent (*n*–butyl lithium (*n*–BuLi) or *tert*–butyl lithium (*t*–BuLi)) in the absence and presence of various Lewis basic ligands followed by trapping with methyl iodide **1** (MeI).[11,12] Figure 2 presents a summarized overview of our site selectivity studies for the benzyl (blue) vs ortho (yellow) positions of various THQ derivatives through the application of several deprotonation strategies.

With THQ **2a** we observed very little selectivity/product in the absence of ligands or in the presence of the additive tetramethylethylenediamine (TMEDA)[13]. Upon introduction of potassium *tert*–butoxide (*t*–BuOK)[14], an increase in methylated products was observed (75%), but the selectivity was very poor with a slight preference for the benzylic position. Selectivity for the benzyl position was greatly increased with *N*, *N*′–dimethylpropyleneurea (DMPU)[15], but the yield of the product was less than 40%. We found that hexamethylphosphoramide (HMPA)[16] provided high conversions; however, the site selectivity was less than ideal with a 3.8 to 1 ratio in favor of the benzylic position. Of note, upon switching to trispyrrolidinephosphoramide (TPPA) both high yields and exclusive site selectivity were observed for the benzylic position. In addition, the 6–

methoxy THQ **2b** substrate provided similar results with the TPPA additive providing both excellent yields and selectivity. Other conditions for metalation of **2b** resulted in either trace amounts of a single product (no additive, TMEDA) or a mixture of constitutional isomers (*t*–BuOK, DMPU, HMPA).

Next, we turned our focus to exploring the site selectivity of N–Aryl substituted THQs **2c**–**d**. The lack of additives and the employment of TMEDA resulted in no product observation for both **2c** and **2d**. Although the employment of *t*–BuOK resulted in methylated products for **2c** in moderate yield, the selectivity was low with the observation of two constitutional isomers with a preference for 1–(*o*–tolyl)–1,2,3,4–tetrahydroquinoline (**2c**–pink).[17] The employment of DMPU resulted in low conversions for both **2c** and **2d**. Importantly, the employment of either HMPA or TPPA resulted in high conversions and selectivity for the benzylic positions in both **2c** and **2d**. Similar to the results observed for the N–Boc and N–Aryl substituted THQs the N–methyl substrate **2e** was successfully methylated in the presence of phosphoramides ligands.

To obtain a more thorough understanding of the selectivity observed with the phosphoramide ligands, THQ isomer **2f** was subject to the same screening conditions as described above and the selectivity was similar in all cases for the benzylic site adjacent to the N–atom with no detectable activation of the remote benzylic group. We concluded that the combined directing and inductive effects of the N–atom within **2f** were too strong to allow for remote positions to be activated within this heterocyclic framework.

The ability to override embedded N–atoms within the THQ scaffold with this protocol and the need for selective functionalization at remote positions inspired us to develop a general deprotonation alkylation procedure.

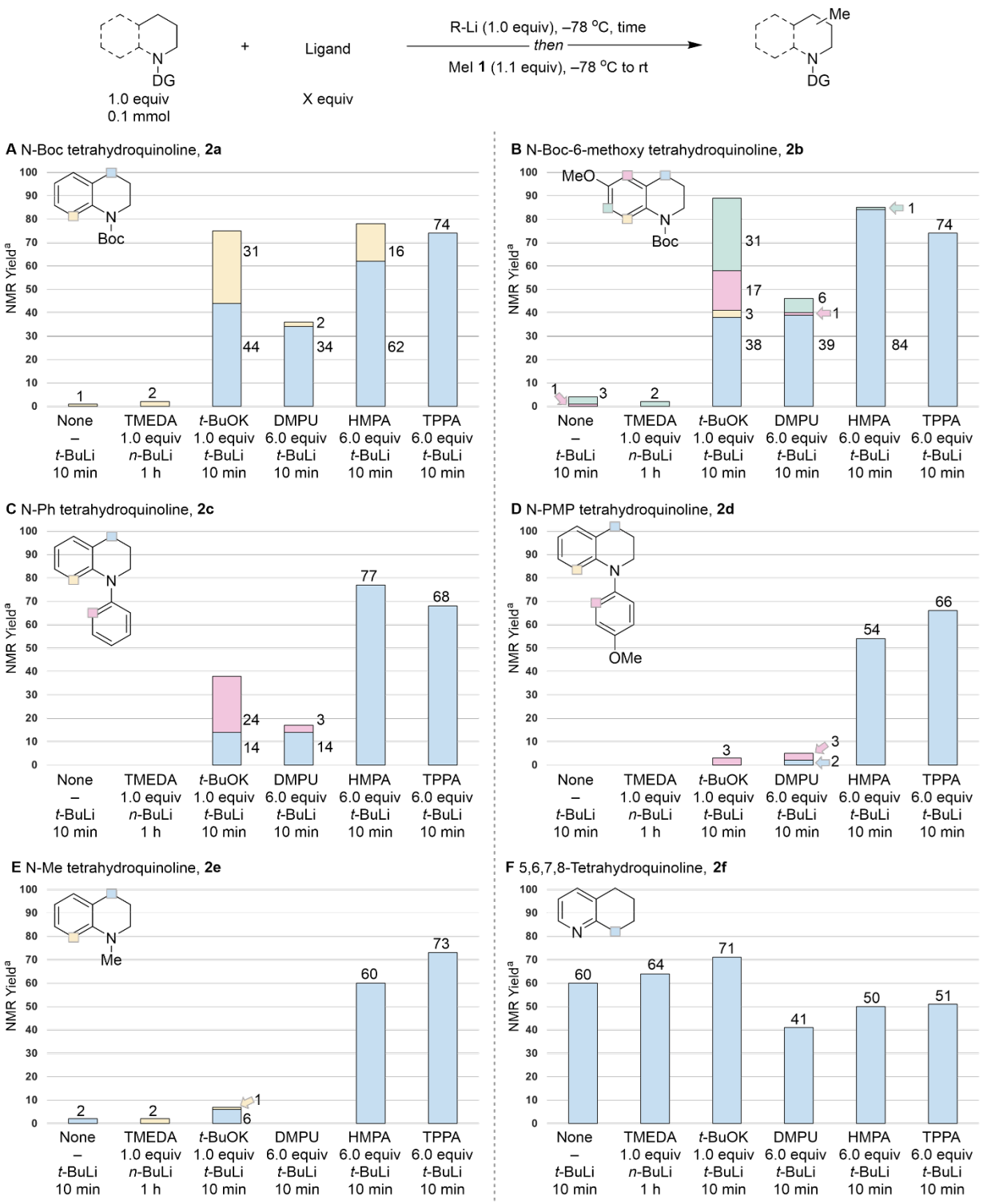


Figure 2. Metalation Site Selectivity Study of tetrahydroquinolines. A) N–Boc THQ **2a** B) 6–Methoxy N–Boc THQ **2b** C) N–Ph THQ **2c** D) N–PMP THQ **2d** E) N–Me THQ **2e** F) 5,6,7,8–THQ **2f.** [a]Yields determined by NMR relative to a 1,3,5-trimethoxybenzene internal standard. Conditions in order from left to right: THQ substrate (1.0 equiv) treated with *t*–BuLi (1.0 equiv) at −78 °C for 10 min before adding MeI **1** (1.1 equiv). THQ substrate (1.0 equiv) treated with TMEDA (1.0 equiv) and *n*–BuLi (1.0 equiv) at −78 °C for 1 h before adding MeI **1** (1.1 equiv).

THQ substrate (1.0 equiv) treated with *t*–BuOK (1.0 equiv) and *t*–BuLi (1.0 equiv) at −78 °C for 10 min before adding MeI **1** (1.1 equiv). THQ substrate (1.0 equiv) treated with DMPU (6.0 equiv) and *t*–BuLi (1.0 equiv) at −78 °C for 10 min before adding MeI **1** (1.1 equiv). THQ substrate (1.0 equiv) treated with HMPA (6.0 equiv) and **t**–BuLi (1.0 equiv) at −78 °C for 10 min before adding MeI **1** (1.1 equiv). THQ substrate (1.0 equiv) treated with TPPA (6.0 equiv) and *t*–BuLi (1.0 equiv) at −78 °C for 10 min before adding MeI **1** (1.1 equiv).

2.2. Development of Deprotonation Alkylation Reaction with Tetrahydroquinolines: Substrate Scope. Encouraged by our initial site selectivity results outlined above, we sought to examine the scope and generality of this process. After a brief optimization of the reaction conditions, a variety of N–substituted THQ substrates **3a**–**d** were successfully alkylated at the benzylic position with *n*–octyl bromide in moderate to quantitative yields using *t*–BuLi and TPPA[18] (Figure 3). Given the successful alkylation of a variety of THQ substrates we next investigated the scope of the alkyl halide coupling partner with the N–Boc substituted THQ **2a**. The primary electrophile **3e** bearing a competing benzylic functional group resulted in near quantitative yields. In addition, organic halides bearing aryl ethers **3f,** tetrahydrofurans **3g**, and acetals **3h** were all well-tolerated under the reaction conditions providing good yields (82 – 89%). Importantly, secondary electrophiles bearing various heterocyclic functional groups such as tetrahydrofurans **3i**, tetrahydropyrans **3j**, and morpholines **3l**, were successfully implemented as well. Of note, 2–bromopropane **3k**, an electrophile prone to E2 elimination under basic conditions, was also found to provide moderate yields (59%) of the alkylation product.

The methoxy ether THQ **3m** was found to provide the trapped product in high yield. Interestingly, morpholine substituted THQ **3n** provided the alkylation product in good yield. In addition, both brominated and chlorinated THQs **3o** and **3p** provided the desired products in low and moderate yields, respectively. These results fall in line with our site selectivity experimental findings that embedded heteroatoms could be overridden within the THQ framework to achieve high selective products.

The usefulness of the direct alkylation of THQ substrates was further demonstrated by preparing analogues of natural products and through the late–stage derivatization of pharmaceuticals (Figure 3). The benzylic analogues of the Hancock alkaloid's Galipinine[19] **3q** and Cuspareine[16] **3r** were synthesized in 79% and 62% yields, respectively. Of note, the phenoxybenzamine[20] **3s** derived chloride was effectively coupled into the THQ framework highlighting that the late derivatization of active pharmaceuticals is achievable. Our success in developing a site selective deprotonation alkylation reaction prompted us to extend our studies to include the development of a transition metal–catalyzed cross–coupling to afford Csp^3–Csp^2 bonds with aromatic halide coupling partners.

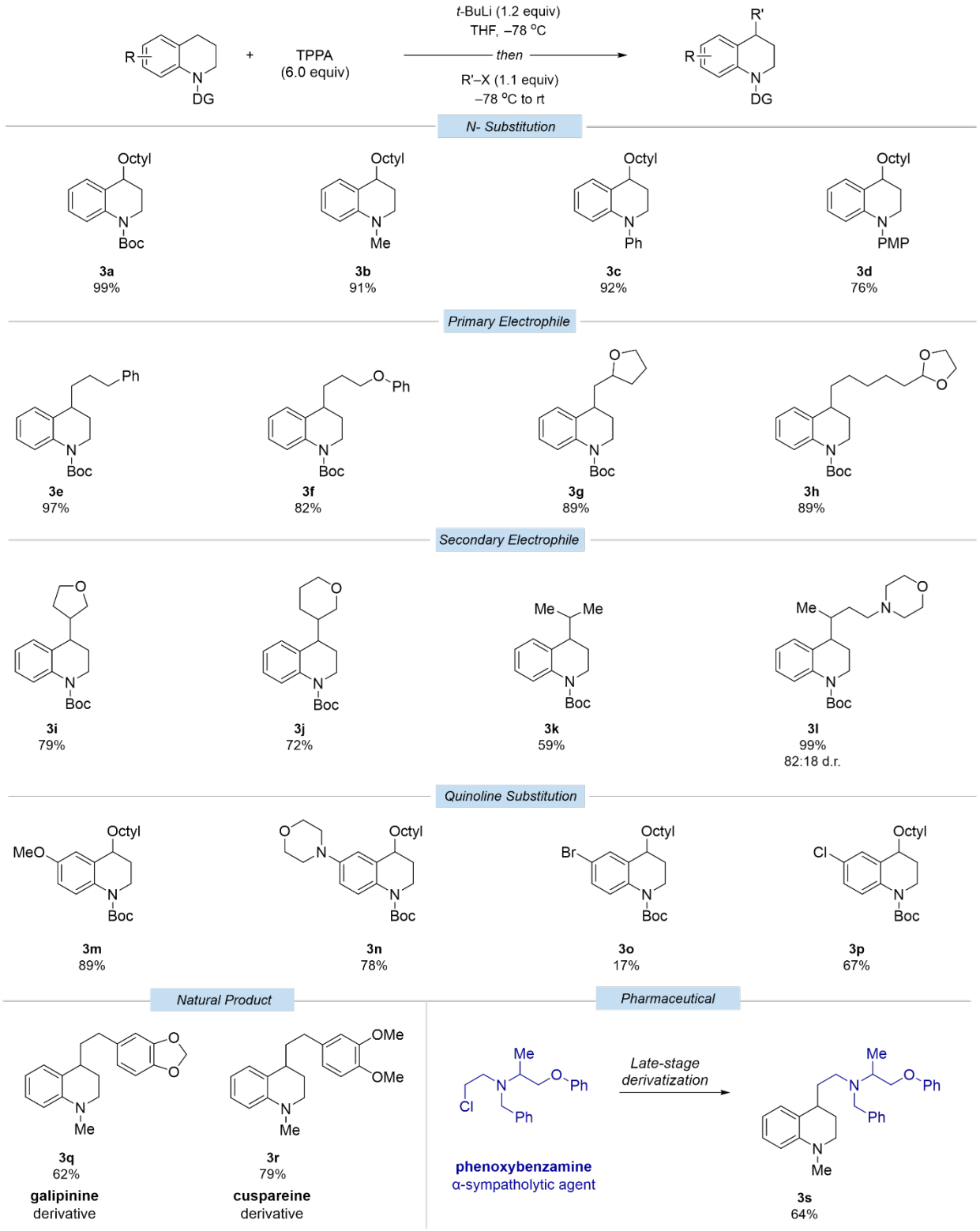


Figure 3. Tetrahydroquinoline Alkylation Scope. Starting with conditions, direct alkylation reaction of N–directing group substrates, **2a** with primary electrophiles, **2a** with secondary electrophiles, **2e** with electrophiles to afford natural product derivatives, and 2e with pharmaceutical electrophile.

2.3. Development of Deprotonation Transition Metal–Catalyzed Cross–Coupling Sequences with Tetrahydroquinolines. *2.3.1. Preliminary Empirical and Mechanistic Experiments.* Although organolithium reagents represent a class of commonly used synthetic building blocks they are seldom harnessed in transition metal catalyzed cross-couplings reactions.[21] This is often attributed to their lower functional group compatibility as compared to their organo–stannane or zinc counterparts as well as their unique ability to undergo rapid lithium halogen exchange reactions with electrophilic halide coupling partners. After a thorough NMR structure elucidation, we determined that our standard reaction conditions lead to separated ion pairs with THQ substrates, such as **4,** of which are underexplored coupling partners in transition metal–catalyzed processes (Figure 4).

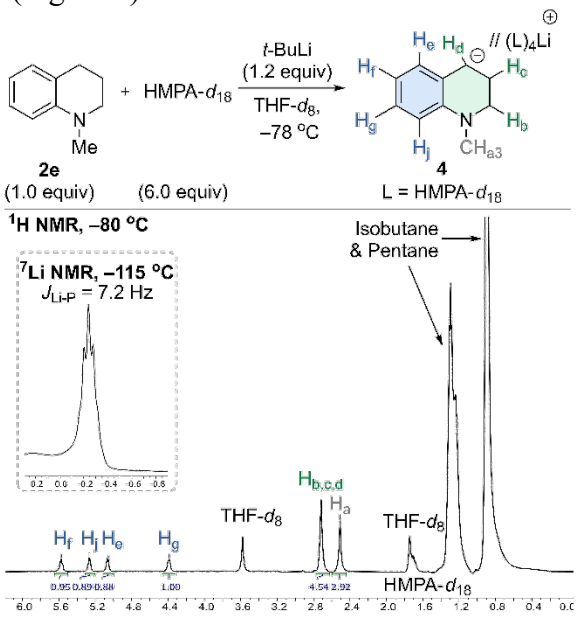
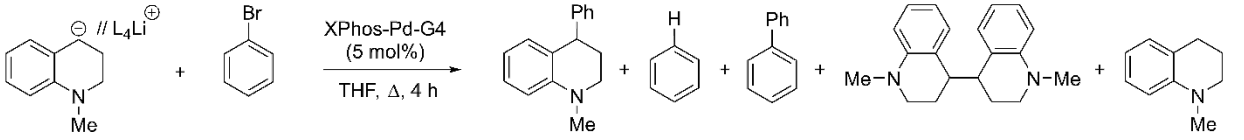


Figure 4. NMR Characterization of THQ-SIP 4 and mechanistic investigation. Scheme of tetrahydroquinoline Separated Ion Pair (THQ-SIP) **4** with ^{1}H NMR spectra at −80 °C and ^{7}Li NMR spectra at −115 °C.

Therefore, our efforts became focused on investigating palladium-catalyzed cross-coupling reactions using THQ–carbanion **4** as the nucleophilic coupling partner and bromobenzene **5a** as the electrophile. After an exhaustive screening campaign, only trace amounts of cross–coupling products were observed; however, in most cases the THQ-carbanion **4** had dimerized to afford **5d** (Figure 5).



Entry		6a	5b	5c	5d	4
1	standard cond.	9%	0%	29%	48%	52%
2	w LiCl	0%	0%	27%	31%	69%

Figure 5. Mechanistic investigation with THQ-SIP 4. Employment of **4** in Cross-Couplings with Br-Ph **5a**. See Supporting Information (S34-S41) for further details.

These results suggested that one of the added reagents was serving as an oxidant and leading to undesired dimerization side reactions. After a series of control experiments it was determined that the addition of bromobenzene **5a** to THQ–carbanion **4** in the absence of transition metals resulted in trace amounts THQ–dimer **5d**, benzene **5b**, and isobutylene *via* ^{1}H and ^{13}C NMR spectroscopy.[22] Therefore, to circumvent the observed undesired processes our efforts switched to developing a deprotonation Negishi cross–coupling sequence due to the more covalent nature of C–Zn bond over the ionic separated ion pair **4**.

2.3.2 Development of Negishi Cross–Coupling Sequences. Prior to undertaking a massive screening campaign to develop a Negishi reaction it was critical to determine if the separated ion pair **4** could undergo transmetalation to zinc(II) halides. In this regard, the comparison of ^{13}C NMR chemical shifts has often proved to be useful in determining changes in bonding especially regarding electron density – thus our initial investigations began by undertaking an NMR study.[23] Upon addition of a THF solution of zinc chloride ($ZnCl_2$) to the THQ–carbanion **4** an immediate up field shift was observed for the benzylic carbon in the ^{13}C NMR spectrum proving support for the intact benzylic-zinc contact ion pair **7** (Figure 6).

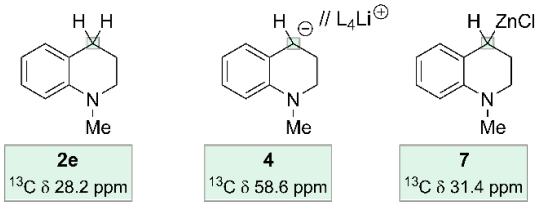


Figure 6. ^{13}C NMR chemical shifts of tetrahydroquinoline species. Left to right: N-Me THQ **2e**, N-Me THQ SIP **4**, and N-Me THQ organozinc **7**.

With the formation of the organozinc THQ **7**, and after a brief optimization of the reaction conditions, a palladium–catalyzed Negishi cross–coupling protocol for Csp^2–Csp^3 bond formation was realized. The finalized reaction conditions were optimized to employ the aromatic halide electrophile (1.0 equiv) as the limiting reagent along with THQ–organozinc **7** (1.5 equiv), and XPhos Pd–G4 (5.0 mol%) as the catalyst (see SI for optimizations). A range of aromatic halides bearing different functional groups were successfully coupled in moderate to excellent yields (Figure 7). For example, phenyl **6a**, 2–toyl **6b**, and 3,5–dimethyl **6c**, phenyl bromides resulted in excellent yields (90 – 98%). In addition, the electron rich aromatic halides incorporating 4–methoxy **6d**, 3–benzodioxole **6e**, and 4–dimethylamino **6f** functional groups provided moderate to high yields (83 – 92%). Moreover, the aromatic halides bearing electron withdrawing substituents such as 3–fluoro **6g**, 4–trifluoromethyl **6h**, and 2–cyano **6i** also provided efficient results (81 – 91%). Extended aromatic systems such as 4–phenyl–benzene **6j**, 1–naphthyl **6k**, and 2–naphthyl **6l** also provided good yields (72 – 89%). The generation of a separated ion pair followed by transmetalation is a viable method to access benzylic nucleophiles for Csp^2–Csp^3 cross–coupling reactions.

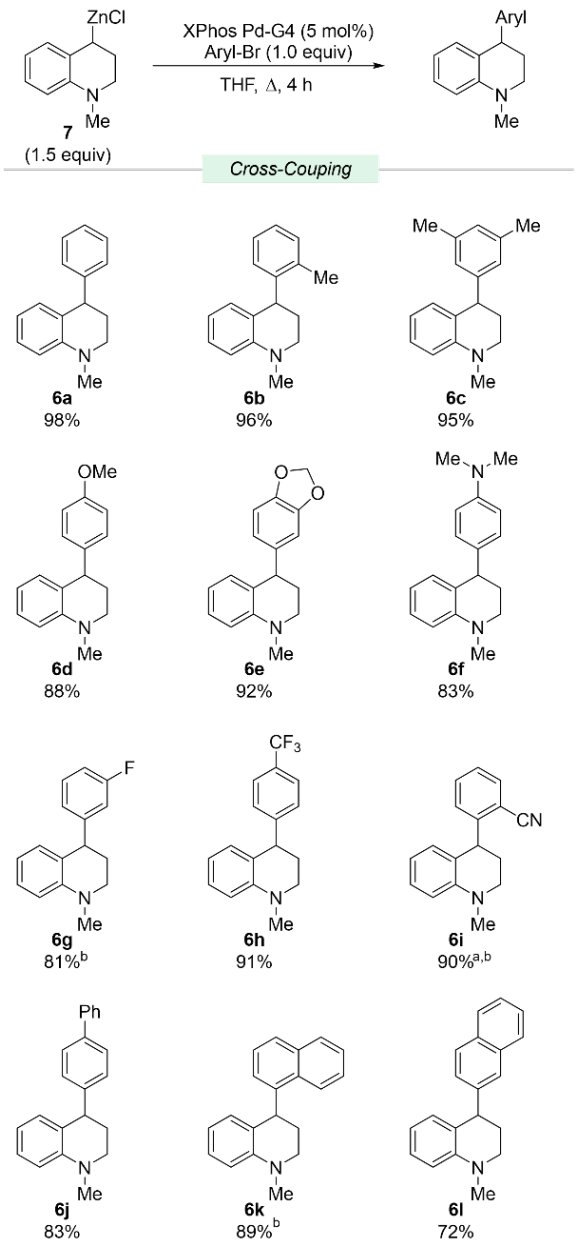


Figure 7. Tetrahydroquinoline Csp^2–Csp^3 Negishi cross–coupling scope. [a]Aryl-chloride starting material was used. [b]Isolated material contains minor amounts (<6%) of constitutional isomers.

3.0 CONCLUSION

In summary, a transition metal free and undirected deprotonation alkylation protocol was established to selectively functionalize the 4–position of tetrahydroquinolines with primary and secondary alkyl halide electrophiles. The key element of this approach is the generation of the highly reactive separated ion pair (*t*-Bu^- // L_4Li^+), which allowed us to bypass the typical substrate directing effects (directed metalation) within the THQ scaffold. Studies revealed that the lack of productive reactivity observed between the freshly generated THQ separated ion pair and aromatic halides under transition metal–catalyzed conditions may be due to unproductive electron transfer

pathways. To circumvent this unproductive pathway, we pursued transmetalation of the freshly generated THQ anions to zinc chloride, and a palladium–catalyzed Negishi cross–coupling reaction was developed to afford 4–aryl substituted THQs with a variety of aromatic halides in moderate to high yields. Not only is this a rare example of undirected metalation conditions for organolithium reagents, but it also attests to the powerful influence of the organolithium aggregate to achieve exclusive site selectivity within heterocyclic scaffolds. Further studies are currently underway to expand the scope of this reaction with respect to both the heterocycle and electrophile components.

ACKNOWLEDGEMENTS
We are grateful for the generous financial support from Texas A&M University and the NIH (Grant No. R35 GM151018). In addition, we are also grateful to the Welch Foundation (A–2081–2021032) which supported our preliminary studies. Andrew V. Nguyen is thanked for preliminary experiments.

Competing Interests: Authors declare that they have no competing interests.

Data and materials availability: All data are available in the main text or the supplementary materials.

Supplementary Materials

Materials and Methods

Figs. S1 to S119

Tables S1 to S17

4.0 References

[1] a) Staub, G. M.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. Aspernomine: A Cytotoxic Antiinsectan Metabolite with a Novel Ring System from the Sclerotia of *Aspergillus Nomius*. *J. Am. Chem. Soc.* **1992**, *114*, 1015–1017. b) Jacquemond-Collet, I.; Hannedouche, S.; Fabre, N.; Fourasté, I.; Moulis, C. Two tetrahydroquinoline alkaloids from *Galipea officinalis*. *Phytochemistry* **1999**, *51*, 1167–1169. c) Magomedov, N. A. Efficient Construction of Cyclopenta[b]quinoline Core of Isoschizozygane Alkaloids via Intramolecular Formal Hetero-Diels−Alder Reaction. *Org. Lett.* **2003**, *5*, 2509–2512. d) Asolkar, R.N.; Schröeder, D.; Heckmann, R.; Lang, S.; Wagner-Döebler, I.; Laatsch, H. Helquinoline, a New Tetrahydroquinoline Antibiotic from *Janibacter limosus* Hel 1. *J. Antibiot.* **2004**, *57*, 17–23. e) Satyanarayana, G.; Pfläesterer, D.; Helmchen, G. Enantioselective Syntheses of Tetrahydroquinolines Based on Iridium-Catalyzed Allylic Substitutions: Total Syntheses of (+)-Angustureine and (–)-Cuspareine. *Eur. J. Org. Chem.* **2011**, *2011*, 6877–6886.

[2] a) Albrecht, B. K.; Anderson, D. L.; Bartberger, M.; Brown, J.; Brown, R.; Chaffee, S. C.; Cheng, Y.; Croghan, M.; Graceffa, R.; Harried, S.; Hitchcock, S.; Hungate, R.; Judd, T.; Kaller, M.; Kreiman, C.; La, D.; Lopez, P.; Masse, C.; Monenschein, H.; Nguyen, T.; Nixey, T.; Patel, V. F.;

Pennington, L.; Weiss, M.; Xue, Q.; Yang, B.; Zhong, W. Beta-Secretase Modulators and Methods of Use. (Amgen Inc.) *US 2007/0185103 A1*, **2007**. b) Guo, T.; Gu, H.; Hobbs, D. W.; Rokosz, L. L.; Stauffer, T. M.; Jacob, B.; Clader, J. W. Design, synthesis, and evaluation of tetrahydroquinoline and pyrrolidine sulfonamide carbamates as γ-secretase inhibitors. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3010–3013. c) Asberom, T.; Bara, T. A.; Clader, J. W.; Greenlee, W. J.; Guzik, H. S.; Josien, H. B.; Li, W.; Parker, E. M.; Pissarnitski, D. A.; Song, L.; Zhang, L.; Zhao, Z. Tetrahydroquinoline sulfonamides as γ-secretase inhibitors. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 205–207. d) Kubota, H.; Sugahara, M.; Furukawa, M.; Takano, M.; Motomura, D. Tetrahydroquinoline Derivatives and A Process for Preparing the Same. (Birch Stewart Kolasch & Birch) *US 2007/0082896 A1*, **2007**. e) Su, D.-S.; Lim, J. J.; Tinney, E.; Wan, B.-L.; Young, M. B.; Anderson, K. D.; Rudd, D.; Munshi, V.; Bahnck, C.; Felock, P. J.; Lu, M.; Lai, M.-T.; Touch, S.; Moyer, G.; DiStefano, D. J.; Flynn, J. A.; Liang, Y.; Sanchez, R.; Prasad, S.; Yan, Y.; Perlow-Poehnelt, R.; Torrent, M.; Miller, M.; Vacca, J. P.; Williams, T. M.; Anthony, N. J. Substituted tetrahydroquinolines as potent allosteric inhibitors of reverse transcriptase and its key mutants. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5119–5123. f) Koochakkhani, S.; Branco, D. S. N.; Alonso, A. V.; Murugesan, A.; Sarkar, P.; Caires, C. J. N.; Devanesan, S.; AlSalhi, M. S.; Candeias, N. R.; Kandhavelu, M. Novel tetrahydroquinoline derivatives induce ROS-mediated apoptosis in glioblastoma cells. *Eur. J. Pharm. Sci.* **2024**, *200*, 106842.

[3] For some reviews see: a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. Recent Progress in the Synthesis of 1,2,3,4=Tetrahydroquinolines. *Tetrahedron* **1996**, *52*, 15031–15070. b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274. c) Marshall, C. M.; Federice, J. G.; Bell, C. N.; Cox, P. B.; Njardarson, J. T An Update on the Nitrogen Heterocycle Compositions and Properties of U.S. FDA-Approved Pharmaceuticals (2013−2023). *J. Med. Chem.* **2024**, *67*, 11622–11655.

[4] a) Reed, J. N.; Rotchford, J.; Strickland, D. Synthesis of 1,2,3,4-Tetrahydroquinolines and 1,2,3,4-Tetrahydro-1,6-Naphthyridines by a Directed Lithiation Reaction. *Tetrahedron Lett.* **1988**, *29*, 5725–5728. b) Snider, B. B.; Ahn, Y.; O'Hare, S. M. Total Synthesis of (±)-Martinellic Acid. *Org. Lett.* **2001**, *3*, 4217–4220. c) Nammalwar, B.; Bunce, R. A. Recent Syntheses of 1,2,3,4-Tetrahydroquinolines, 2,3-Dihydro-4(1H)-quinolinones and 4(1H)-Quinolinones using Domino Reactions. *Molecules* **2014**, *19*, 204–232. d) Zhou, W.; Tian, X.; Zhen, Y.; Wang, A.; He, M.; Sun, S. Efficiently Constructing Tetrahydroquinolines through Cascade Radical Additions and Cyclizations under the Catalysis of Cu^{I}. *ChemistrySelect* **2021**, *6*, 5926–5931. e) El-Shahat, M. Advances in the reduction of quinolines to 1,2,3,4-tetrahydroquinolines. *J. Heterocycl. Chem.* **2022**, *59*, 399–421. f) Lemos, B. C.; Venturini Filho, E.; Fiorot, R. G.; Medici, F.; Greco, S. J.; Benaglia, M. Enantioselective Povarov Reactions: An Update of a Powerful Catalytic Synthetic Methodology. *Eur. J. Org. Chem.* **2022**, *2022*, e202101171. g) Ishigaki, S.; Nagashima, Y.; Yukimori, D.; Tanaka, J.; Matsumoto, T.; Miyamoto, K.; Uchiyama, M.; Tanaka, K. Dearomative triple elementalization of quinolines driven by visible light. *Nat. Commun.* **2023**, *14*, 652. h) Lee, S. H.; Chi, H. M. HFIP-Empowered One-Pot Synthesis of C4-Aryl-Substituted Tetrahydroquinolines with Propargylic Chlorides and Anilines. *Org. Lett.* **2023**, *25*, 1083–1087. i) Wu, J.; Tan, X.; Wu, W.; Jiang, H. Palladium-catalyzed cascade of *aza*-Wacker and Povarov reactions of aryl amines and 1,6-dienes for hexahydro-cyclopenta[*b*] quinoline framework. *Nat.*

Commun. **2024**, *15*, 6776. j) Mandal, A.; Khan, A. T. Recent advancement in the synthesis of quinoline derivatives via multicomponent reactions. *Org. Biomol. Chem.* **2024**, *22*, 2339–2358.

[5] Asymmetric Examples: a) Kang, Y. K.; Kim, S. M.; Kim, D. Y. Enantioselective Organocatalytic C–H Bond Functionalization via Tandem 1,5–Hydride Transfer/Ring Closure: Asymmetric Synthesis of Tetrahydroquinolines. *J. Am. Chem. Soc.* **2010**, *132*, 11847–11849. b) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. Selective Activation of Enantiotopic C(sp^3)–Hydrogen by Means of Chiral Phosphoric Acid: Asymmetric Synthesis of Tetrahydroquinoline Derivatives. *J. Am. Chem. Soc.* **2011**, *133*, 6166–6169. c) Hopkins, B. A.; Wolfe, J. P. Enantioselective synthesis of tetrahydroquinolines, tetrahydroquinoxalines, and tetrahydroisoquinolines *via* Pd–Catalyzed alkene carboamination reactions. *Chem. Sci.* **2014**, *5*, 4840–4844. d) Anderson, J. C.; Barham, J. P.; Rundell, C. D. An Asymmetric Intramolecular Conjugate Addition nitro-Mannich route to *cis*-2-aryl-3-nitrotetrahydroquinolines. *Org. Lett.* **2015**, *17*, 4090–4093. e) Du, Y.-L.; Hu, Y.; Zhu, Y.-F.; Tu, X.-F.; Han, Z.-Y.; Gong, L.-Z. *J.* Chiral Gold Phosphate Catalyzed Tandem Hydroamination/Asymmetric Transfer Hydrogenation Enables Access to Chiral Tetrahydroquinolines. *Org. Chem.* **2015**, *80*, 4754–4759. f) Zhang, Z.; Du, H. Cis-Selective and Highly Enantioselective Hydrogenation of 2,3,4Trisubstituted Quinolines. *Org. Lett.* **2015**, *17*, 2816–2819. g) Leth, L. A.; Glaus, F.; Meazza, M.; Fu, L.; Thøgersen, M. K.; Bitsch, E. A.; Jørgensen, K. A. Decarboxylative [4+2] Cycloaddition by Synergistic Palladium and Organocatalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 15272–15276. h) Liu, R.-R.; Li, B.-L.; Lu, J.; Shen, C.; Gao, J.-R.; Jia, Y.-X. Palladium/L–Proline–Catalyzed Enantioselective α–Arylative Desymmetrization of Cyclohexanones. *J. Am. Chem. Soc.* **2016**, *138*, 5198–5201. i) Wang, Y.; Liu, Y.; Zhang, D.; Wei, H.; Shi, M.; Wang, F. Enantioselective Rhodium-Catalyzed Dearomative Arylation or Alkenylation of Quinolinium Salts. *Angew. Chem., Int. Ed.* **2016**, *55*, 3776–3780. j) Lim, C. S.; Quach, T. T.; Zhao, Y. Enantioselective Synthesis of Tetrahydroquinolines by Borrowing Hydrogen Methodology: Cooperative Catalysis by an Achiral Iridacycle and aChiral Phosphoric Acid. *Angew. Chem., Int. Ed.* **2017**, *56*, 7176–7180. k) Zhu, Y.; Li, B.; Wang, C.; Dong, Z.; Zhong, X.; Wang, K.; Yan, W.; Wang, R. Asymmetric synthesis of CF_3-containing tetrahydroquinoline *via* a thiourea-catalyzed cascade reaction. *Org. Biomol. Chem.* **2017**, *15*, 4544–4547. l) Denmark, S. E.; Chi, H. M. Catalytic, Enantioselective, Intramolecular Sulfenoamination of Alkenes with Anilines. *J. Org. Chem.* **2017**, *82*, 3826–3843. m) Zhao, Z.-B.; Wang, J.; Zhu, Z.-H.; Chen, M.-W.; Zhou, Y.-G. Enantioselective Synthesis of 2-Functionalized Tetrahydroquinolines through Biomimetic Reduction. *Org. Lett.* **2021**, *23*, 9112–9117. n) Chen, M.-W.; Wu, B.; Liu, Z.; Zhou, Y.-G. Biomimetic Asymmetric Reduction Based on the Regenerable Coenzyme NAD(P)H Models. *Acc. Chem. Res.* **2023**, *56*, 2096–2109.

[6] a) Beak, P.; Snieckus, V. Directed Lithiation of Aromatic Tertiary Amides: An Evolving Synthetic Methodology for Polysubstituted Aromatics. *Acc. Chem. Res.* **1982**, *15*, 306–312. b) Beak, P.; Meyers, A. I. Stereo– and Regiocontrol by Complex Induced Proximity Effects: Reactions of Organolithium Compounds. *Acc. Chem. Res.* **1986**, *19*, 356–363. c) Tang, R.-Y.;Li, G. ;Yu, J.-Q. Conformation–induced remote *meta*–C–H activation of amines. *Nature* **2014**, *507*, 215–220. d) Carter, N.; Li, X.; Reavey, L.; Meijer, A. J. H. M.; Coldham, I. Synthesis and kinetic resolution of substituted tetrahydroquinolines by lithiation then electrophilic quench. *Chem. Sci.* **2018**, *9*, 1352–1357.

[7] a) Hamann, L. G.; Huguchi, R. I.; Zhi, L.; Edwards, J. P.; Wang, X.-N.; Marschke, K. B.; Kong, J. W.; Farmer, L. J.; Jones, T. K. Synthesis and Biological Activity of a Novel Series of Nonsteroidal, Peripherally Selective Androgen Receptor Antagonists Derived from 1,2-Dihydropyridono[5,6-g]quinolines. *J. Med. Chem.* **1998**, *41*, 623–639. b) Dhar, A.; Liu, S.; Klucik, J.; Berlin, K. D.; Madler, M. M.; Lu, S.; Ivey, R. T.; Zachies, D.; Brown, C. W.; Nelson, E. C.; Birckbichler, P. J.; Benbrook, D. M. Synthesis, Structure-Activity Relationships, and RARγ-Ligand Interactions of Nitrogen Heteroarotinoids. *J. Med. Chem.* **1999**, *42*, 3602–3614. c) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. Intramolecular Arylation Reactions of Alkenes: A Flexible Approach to Chromans and Tetrahydroquinoline Derivatives. *J. Am. Chem. Soc.* **2004**, *126*, 3416–3417. d) Lu, H.-H.; Liu, H.; Wu, W.; Wang, X.-F.; Lu, L.-Q.; Xiao, W.-J. Catalytic Asymmetric Intramolecular Hydroarylations of ω-Aryloxy- and Arylamino-Tethered α,β-Unsaturated Aldehydes. *Chem. – Eur. J.* **2009**, *15*, 2742–2746. e) Astudillo Saavedra, L.; Vallejos, G. C.; Kouznetsov, V. V.; Gutierrez, M. C.; Meléndez Gómez, C. M.; Vargas Méndez, L. Y.; Bermúdez Jaimes, J. H. Synthesis of New Diversely Linked Biquinoline Derivatives by Multicomponent Imino-Diels–Alder Cycloaddition and Intramolecular Friedel–Crafts Cyclization. *Synthesis* **2010**, *4*, 593–600. f) Vargas Méndez, L. Y.; Zacchino, S. A.; Kouznetsov, V. V. Synthesis of New 4-Methyl-2-(4-pyridyl)-1,2,3,4-tetrahydroquinolines as Potent Antifungal Compounds. *J. Braz. Chem. Soc.* **2010**, *21*, 105–111. g) Patil, D. V.; Cavitt, M. A.; Grzybowski, P.; France, S. An efficient synthesis of hydropyrido[1,2-α]indole-6(7H)-ones *via* an In(III)-catalyzed tandem cyclopropane ring-opening/Friedel–Crafts alkylation sequence. *Chem. Commun.* **2011**, *47*, 10278–10280. h) Wilson, J. E. Diastereoselective synthesis of tetrahydroquinolines via a palladium-catalyzed Heck–Suzuki cascade reaction. *Tetrahedron Lett.* **2012**, *53*, 2308–2311. i) Compain, G.; Bonneau, C.; Martin-Mingot, A.; Thibaudeau, S. Selective Anti-Markovnikov Cyclization and Hydrofluorination Reaction in Superacid HF/SbF_5: A Tool in the Design of NitrogenContaining (Fluorinated) Polycyclic Systems. *J. Org. Chem.* **2013**, *78*, 4463–4472. j) Martínez-Estíbalez, U.; García-Calvo, O.; Ortiz-De-Elguea, V.; Sotomayor, N.; Lete, E. Intramolecular Mizoroki–Heck Reaction in the Regioselective Synthesis of 4-Alkylidene-tetrahydroquinolines. *Eur. J. Org. Chem.* **2013**, *2013*, 3013–3022. k) Liu, L.; Wang, C.; Liu, Q.; Kong, Y.; Chang, W.; Li, J. Copper(II) Trifluoromethanesulfonate Catalyzed Hydroamination Cyclization–Dimerization Cascade Reaction of Homopropargylic Amines for the Construction of Complex Fused Nitrogen Containing Tetracycles. *Eur. J. Org. Chem.* **2016**, *2016*, 3684–3690.

[8] a) Yin, Y.; Zhao, G. Synthesis of Indolines And Quinoline *via* Cyclization of N-Arylsulfonyl-2-Allylanilines Catalyzed by Brønsted Acid. *Heterocycles* **2006**, *68*, 23–31. b) Patil, N. T.; Wu, H.; Yamamoto, Y. A Route to 2-Substituted Tetrahydroquinolines via Palladium-Catalyzed Intramolecular Hydroamination of Anilino-alkynes. *J. Org. Chem.* **2007**, *72*, 6577–6579. c) Kothandaraman, P.; Foo, S. J.; Chang, P. W. H. Gold-Catalyzed Intramolecular Allylic Amination of 2-Tosylaminophenylprop-1-en-3-ols. A Concise Synthesis of (±)-Angustureine. *J. Org. Chem.* **2009**, *74*, 5947–5952. d) Jiang, F.; Wu, Z.; Zhang, W. Pd(II)-catalyzed oxidative cyclization reaction for the preparation of 2-substituted 1,2,3,4-tetrahydroquinolines with halide functionality. *Tetrahedron* **2011**, *67*, 1501–1505. e) Trost, B. M.; O'Boyle, B. M.; Torres, W.; Ameriks, M. K. Development of a Flexible Strategy towards FR900482 and the Mitomycins. *Chem. – Eur. J.* **2011**, *17*, 7890–7903. f) Chowdhury, C.; Das, B.; Mukherjee, S.; Achari, B. Palladium-Catalyzed Approach for the General Synthesis of (E)-2Arylmethylidene-*N*-tosylindolines and (E)-2-Arylmethylidene-*N*-tosyl/nosyltetrahydroquinolines: Access to 2-Substituted Indoles and

Quinolines. *J. Org. Chem.* **2012**, *77*, 5108–5119. g) Wang, X.; Wu, Z.; Zhu, X.; Ye, C.; Jiang, F.; Zhang, W. A Pd(II)-Catalyzed Oxidative Cyclization for the Preparation of Aryl-Fused Six-Membered Nitrogen Heterocycles with 2-Acetoxy Functionality. *Chin. J. Chem.* **2013**, *31*, 132–138. h) Ghosh, M.; Dhara, S.; Nuree, Y.; Ray, J. K. Synthesis of bis-exocyclic conjugated diene containing 1,2,3,4-tetrahydroquinoline derivatives *via* palladium-catalyzed intramolecular Heck cyclization. *RSC Adv.* **2014**, *4*, 41561–41564.

[9] a) Kerrick, S. T.; Beak, P. Asymmetric Deprotonations: Enantioselective Syntheses of 2–Substituted (*tert*–Butoxycarbonyl)pyrrolidines. *J. Am. Chem. Soc.* **1991**, *113*, 9708–9710. b) Beak, P.; Lee, W. K. α–Lithioamine Synthetic Equivalents: Syntheses of Diastereoisomers from Boc Derivatives of Cyclic Amines. *J. Org. Chem.* **1993**, *58*, 1109–1117. c) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. Complex Induced Proximity Effects: Enantioselective Syntheses Based on Asymmetric Deprotonations of *N*–Boc–pyrrolidines. *J. Am. Chem. Soc.* **1994**, *116*, 3231–3239. d) Beak, P.; Basu, A.; Gallagher, D. J.; Park. Y. S.; Thayumanavan, S. Regioselective, Diastereoselective, and Enantioselective Lithiation–Substitution Sequences: Reaction Pathways and Synthetic Applications. *Acc. Chem. Res.* **1996**, *29*, 552–560.

[10] Crockett, M. P.; Piña, J.; Gogoi, A. R.; Lalisse, R. F.; Nguyen, A. V.; Gutierrez, O.; Thomas, A. A. Breaking the *tert*–Butyllithium Contact Ion Pair: A Gateway to Alternate Selectivity in Lithiation Reactions. *J. Am. Chem. Soc.* **2023**, *145*, 10743–10755.

[11] Although the directed metalation appears low in the absence of Lewis basic additives, we cannot rule out the possibility that metalation is not occurring on the aromatic ring due to the choice of electrophile.

[12] Please see supplementary material (S42–S76) for details.

[13] a) Bauer, W.; Schleyer, P. v. R. Mechanistic Evidence for Ortho–Directed Lithiations from One– and Two–Dimensional NMR Spectroscopy and MNDO Calculations. *J. Am. Chem. Soc.* **1989**, 7191–7198. b) Collum, D. B. Is *N,N,N',N'*–Tetramethylethylenediamine a Good Ligand for Lithium? *Acc. Chem. Res.* **1992**, *25*, 448–454. c) Hoffmann, D.; Collum, D. B. Binding of Diamines to *n*–Butyllithium Dimers: Relative Solvation Energies and Evidence of Correlated Solvation *J. Am. Chem. Soc.* **1998**, *120*, 5810–5811.

[14] Schlosser, M. Zur Aktivierung Lithiumorganischer Reagenzien *J. Organomet. Chem.* **1967**, *8*, 9–16.

[15] Mukhopadhyay, T.; Seebach, D. 39. Substitution of HMPT by the Cyclic Urea DMPU as a Cosolvent for Highly Reactive Nucleophiles and Bases. *Helv. Chim. Acta* **1982**, *65*, 385–391.

[16] Shimano, M.; Meyers, A. I. α–Ethoxyvinyllithium•HMPA. Further Studies on its Unusual Basic Properties. *Tetrahedron Lett.* **1997**, *38*, 5415–5418.

[17] Please see supplementary material (S47, S51–S53) for details.

[18] TPPA was chosen over HMPA due to its high selectivity and a non–mutagenic alternative. See Ref: Coste, J.; Le-Nguyen, D.; Castro, B. PyBOP®: A New Peptide Coupling Reagent Devoid of Toxic By-Product *Tetrahedron Lett.* **1990**, *31*, 205–208.

[19] Jacquemond-Collet, I.; Benoit-Vical, F.; Mustofa; Valentin, A.; Stanislas, E.; Mallié, M.; Fourasté, I. Antiplasmodial and Cytotoxic Activity of Galipinine and other Tetrahydroquinolines from *Galipea officinalis*. *Planta Med.* **2002**, *68*, 68–69.

[20] Tiwari, S. K.; Chennuri, R.; Samala, B.; Kintali, V. R.; Meenakshisunderam, S. A Process for the Preparation of Phenoxybenzamine. (Aurobindo Pharma Limited), *C07D 295/088*, **2018**.

[21] a) Murahashi, S.-I.; Yamamura, M.; Yanagisawa, K.; Mita, N.; Kondo, K. Stereoselective Synthesis of Alkenes and Alkenyl Sulfides from Alkenyl Halides Using Palladium and Ruthenium Catalysts. *J. Org. Chem.* **1979**, *44*, 2408–2416. b) Nagaki, A.; Kenmoku, A.; Moriwaki, Y.; Hayashi, A.; Yoshida, J. I. Cross–Coupling in a Flow Microreactor: Space Integration of Lithiation and Murahashi Coupling**. *Angew. Chem., Int. Ed.* **2010**, *49*, 7543–7547. c) Hornillos, V.; Giannerini, M.; Vila, C.; Fañanás-Mastral, M.; Feringa, B. L. Catalytic Direct Cross–Coupling of Organolithium Compounds with Aryl Chlorides. *Org. Lett.* **2013**, *15*, 5114–5117. d) Vidal, C.; García-Álvarez, J.; Hernán-Gómez, A.; Kennedy, A. R.; Hevia, E. Introducing Deep Eutectic Solvents to Polar Organometallic Chemistry: Chemoselective Addition of Organolithium and Grignard Reagents to Ketones in Air**. *Angew. Chem., Int. Ed.* **2014**, *53*, 5969–5973. e) Jia, Z.; Liu, Q.; Peng, X.-S.; Wong, H. N. C. Iron–catalysed cross–coupling of organolithium compounds with organic halides. *Nat. Commun.* **2016**, *7*, 10614. f) Pinxterhuis, E. B.; Giannerini, M.; Hornillos, V.; Feringa, B. L. Fast, greener and scalable direct coupling of organolithium compounds with no additional solvents. *Nat. Commun.* **2016**, *7*, 11698. g) Visser, P.; Feringa, B. L. Organogelation enables fast organolithium cross-coupling reactions in air†. *Chem. Commun.* **2023**, *59*, 5539–5542.

[22] To completely elucidate the exact mechanistic picture that leads to this product distribution more mechanistic experimentation must be conducted to understand the increase in dimerization product yields under catalytic conditions. Please see supplementary material for details.

[23] a) Boche, G.; Bosold, F.; Lohrenz, J. C. W.; Opel, A.; Zulauf, P. α–Oxygen–Substituted Organolithium Compounds and their Carbenoid Nature: Reactions with RLi and other Nucleophiles, Experimental and IGLO–Calculated ^{13}C–NMR Shifts of the Carbenoid C Atom. *Chem. Ber.* **1993**, *126*, 1873–1885. b) Fleckenstein, J. E.; Koszinowski, K. Lithium Organozincate Complexes $LiRZnX_2$: Common Species in Organozinc Chemistry. *Organometallics* **2011**, *30*, 5018–5026. c) Hanada, E. M.; Jess, K.; Blum, S. A. Mechanism of an Elusive Solvent Effect in Organozinc Reagent Synthesis. *Chem. – Eur. J.* **2020**, *26*, 15094–15098.