

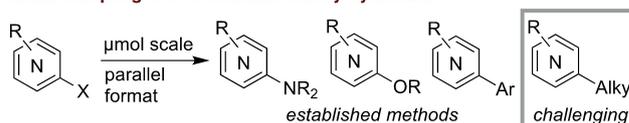
ChemBead Enabled High-Throughput Cross-Electrophile Coupling Reveals a New Complementary Ligand

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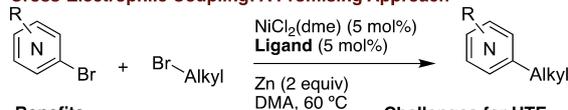
Dedicated to the memory of Donald C. Batesky, who first proposed the use of the BpyCam class of ligands.

Abstract: High-throughput experimentation (HTE) methods are central to modern medicinal chemistry. While many HTE approaches to C–N and Csp²–Csp² bonds are available, options for Csp²–Csp³ bonds are limited. We report here how the adaptation of nickel-catalyzed cross-electrophile coupling of aryl bromides with alkyl halides to HTE is enabled by AbbVie ChemBeads technology. By using this approach, we were able to quickly map out the reactivity space at a global level with a challenging array of 3 × 222 micromolar reactions. The observed hit rate (56%) is competitive with other often-used HTE reactions and the results are scalable. A key to this level of success was the finding that bipyridine 6-carboxamide (BpyCam), a ligand that had not previously been shown to be optimal in any reaction, is as general as the best-known ligands with complementary reactivity. Such “cryptic” catalysts may be common and modern HTE methods should facilitate the process of finding these catalysts.

Cross-Coupling in HTE-Enabled Library Synthesis



Cross-Electrophile Coupling: A Promising Approach



Benefits

- stable starting materials
- large pool of substrates

Challenges for HTE

- Zn⁰ leads to stirring challenges
- Zn⁰ requires solids-handling
- limited conditions reported

ChemBeads Enable HTE Cross-Electrophile Coupling

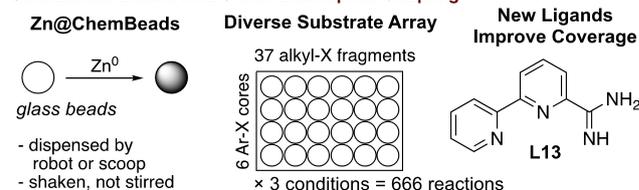


Figure 1. ChemBeads-enabled high-throughput cross-electrophile coupling.

High-throughput experimentation (HTE) methods have become a key component of drug development,^[1] facilitating the rapid exploration of structure-activity relationships (SAR) in medicinal chemistry and the rapid optimization of reactions in process development.^[2] In industrial and academic labs, HTE methods are increasingly used in reaction optimization,^[3] reaction discovery,^[4] and the discovery of new ligands.^[5] Translation of methods from academic labs to medicinal chemistry can be accelerated by HTE assessments using arrays of representative substrates tested against arrays of the best available catalysts and conditions.^[6] To date, most of the methods adapted to HTE at AbbVie for medicinal chemistry have been C–N, C–O, and Csp²–Csp² bond-forming reactions (Figure 1).^[7] HTE methods to explore SAR while increasing Csp³ character in molecules would

be valuable because increased saturation generally improves parameters important to drug discovery.^[8]

Nickel-catalyzed cross-electrophile coupling of alkyl electrophiles with aryl electrophiles^[9] has become an increasingly used approach to the formation of Csp²–Csp³ bonds in the past decade^[10,11] because it is compatible with many functional groups and the pool of available substrates is large (Figure 1).^[12] The stability and availability of organic electrophiles is especially attractive for HTE in medicinal chemistry, where many analogs must be generated quickly. A recently published survey of available methods for Csp³–Csp² cross-coupling in medicinal chemistry demonstrated the potential of cross-electrophile coupling in library synthesis and its complementarity to other approaches.^[13] In that study, however, the scope of the survey was limited by the format – standard parallel library synthesis in 4 mL vials at 0.1 mmol scale. HTE library generation is generally conducted on orders of magnitude smaller scale (micromole to nanomole) because only small amounts of material are needed for initial screening and, in early stages of a project, available starting materials may be limited.

The primary challenge to implementing cross-electrophile coupling chemistry in an HTE format suitable for medicinal chemistry applications at AbbVie was the heterogeneous nature of these reactions – dispensing the solid metal reductants (Zn

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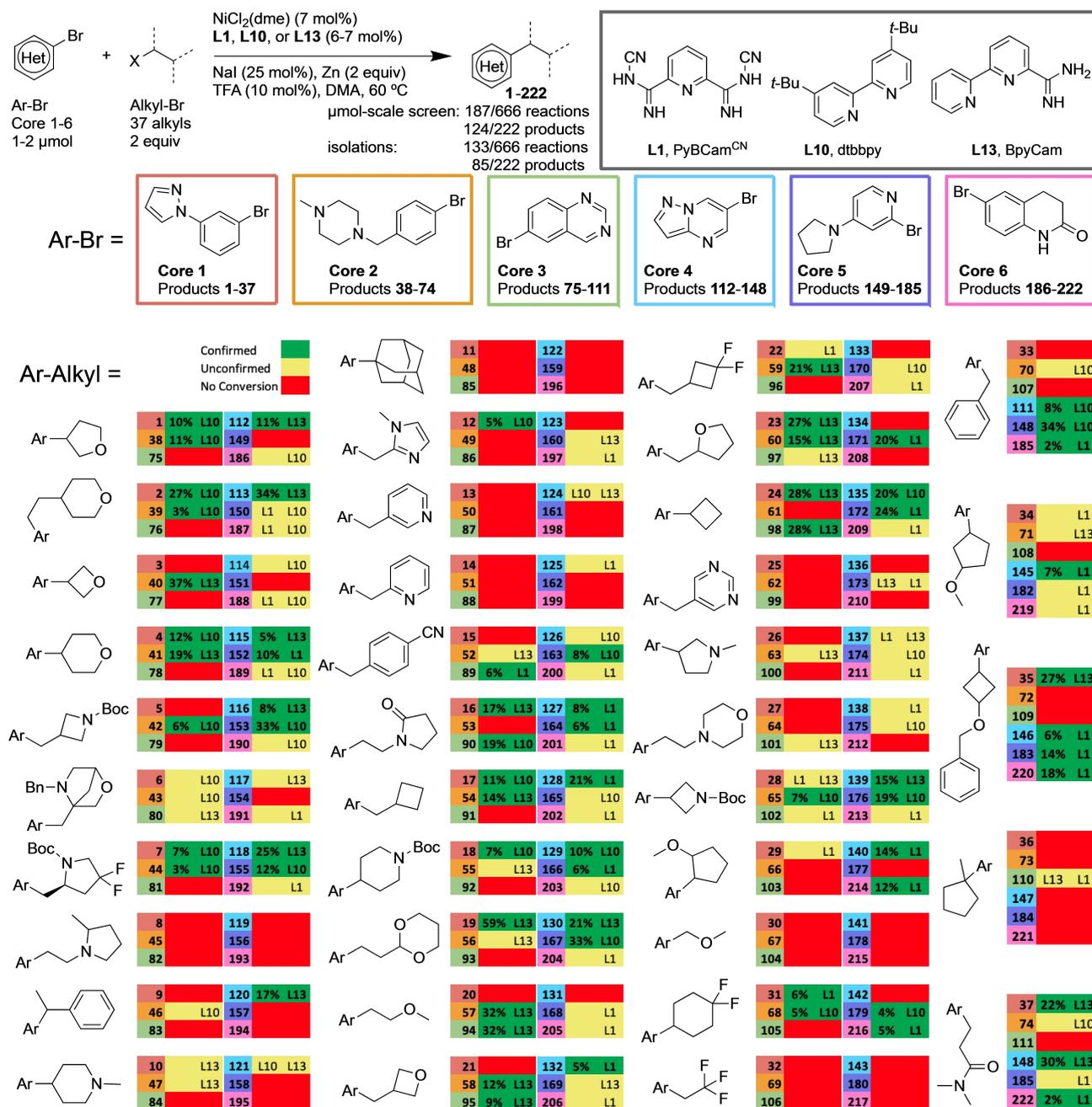
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or Mn powders) in parallel at micromolar scale^[14] and efficiently stirring the reactions in multi-well plates.^[15,16] The challenges of heterogeneity have motivated the development of homogeneous conditions that employ organic terminal reductants,^[17] sometimes using photoredox co-catalysis^[13,18] or electrochemistry^[19] to help drive the reaction. While avoiding some of the challenges of dispensing and stirring, these approaches often have different scope than metal-reductant conditions and some could be a challenge to adapt to parallel

plates.^[13] We report here the successful application of the AbbVie ChemBeads HTE platform^[20] to cross-electrophile coupling, providing a general solution to Csp²–Csp³ bond formation and facilitating the discovery of a new, general ligand (Scheme 1).

To overcome the challenges associated with weighing solids and stirring heterogeneous reactions, we turned to our AbbVie ChemBeads technology. While we had not previously coated beads with malleable metals,^[21] we found that Zn coats on glass



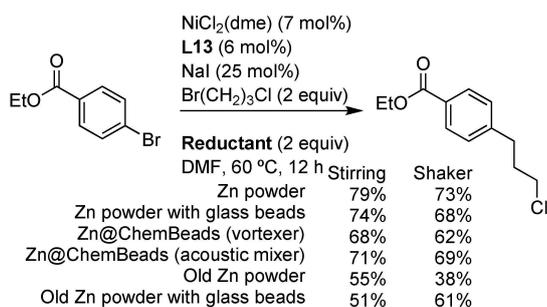
Scheme 1. Results of HTE library survey of 222 different products utilizing ChemBeads and three different cross-electrophile coupling catalysts (L1, L10, L13). Green denotes molecular ion for product observed by LC-MS at 10 μmol scale and verified by isolation at 100 μmol scale; Yellow denotes molecular ion observed at 10 μmol scale, but isolation at 100 μmol scale did not provide > 95% pure product; Red denotes no ion observed. Yields reported are isolated yields after isolation by mass-directed HPLC. Ligands only noted if a large difference was noted or if the product was isolated. No noted ligand means that all three ligands worked well. See Supporting Information for experimental details.

beads well (4.8 mass %, “Zn@ChemBeads”), as long as activated Zn powder is used. While an acoustic mixer is generally required for reliable coating, Zn coated well even using a simple vortexer. In addition, we found that shaking plates on a modified orbital shaker (Torrey Pines SC20) with glass beads is a general replacement for the use of specialized stirrers and micro stir bars (Scheme 2A). Pre-coated ChemBeads are still advantageous because they simplify working on μmol scale and with solid-handling robots or calibrated scoops.

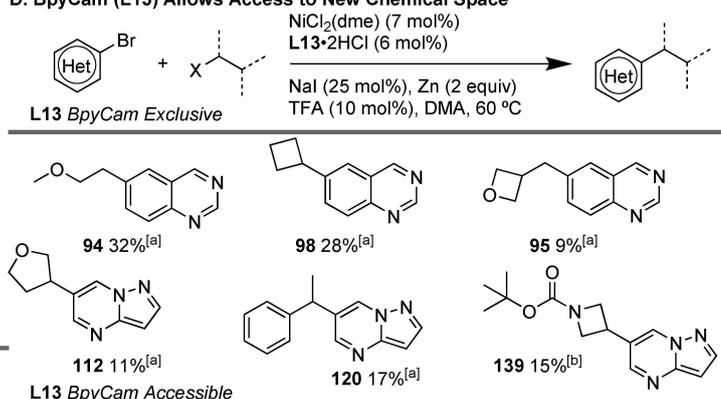
In order to examine the suitability of nickel-catalyzed coupling of aryl halides with alkyl halides for medicinal chemistry applications, an array of 222 different products was chosen to represent the diversity of aryl and alkyl coupling partners of interest to medicinal chemistry: 6 aryl halides \times 37 alkyl halides (Scheme 1). While a wide array of heteroaryl halides have been explored recently in cross-electrophile coupling,^[22] alkyl halides have been more limited: even in our recent study,^[13] 40% of the 20 alkyl bromides tested were simple hydrocarbons. In this study, we emphasized alkyl bromides of interest to medicinal chemistry that we expected

to be particularly challenging, including: neopentyl substrates,^[23] tertiary alkyl substrates,^[24] substrates with β -leaving groups,^[25] substrates prone to methylcyclobutane radical rearrangement,^[26] reactive heteroarylmethyl chlorides,^[27] basic tertiary amines,^[28] and precursors to valuable four-membered rings.^[29] For the HTE experiments run at AbbVie, catalysts and additives were coated onto beads, substrates were dispensed as solutions, and plates were set up using a robotic solid handling system (Chemspeed Technologies). Even without a robot, Zn@ChemBeads simplify small-scale reaction setup in parallel because a calibrated scoop can be used in place of individual weighing or inaccurate zinc slurries. Initially, we chose our published optimal conditions for the coupling of aryl bromides with alkyl bromides (L = 4,4'-di-*tert*-butyl-2,2'-bipyridine, dtbbpy, L10)^[9] and heteroaryl bromides with alkyl bromides (L = 2,6-bis(*N*-cyanocarboxamide)pyridine, PyB-Cam^{CN}, L1).^[22b] Preliminary examination of optimal ligands from published reports (phenanthrolines, bipyridines, pyridine carboxamides, terpyridines) and exchanging Mn for Zn did not provide substantial improvements in the observed hit rate

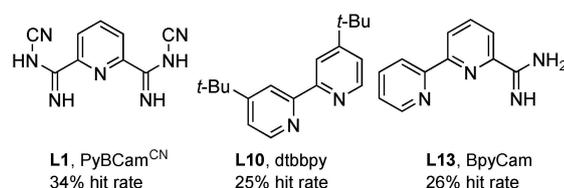
A. Zn@ChemBeads vs Zn Powder



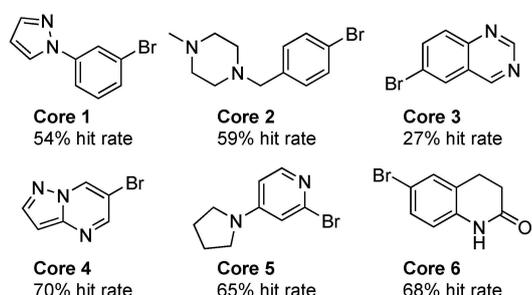
D. BpyCam (L13) Allows Access to New Chemical Space



B. Coverage by Ligand Class



C. Coverage By Aryl Core



Scheme 2. Analysis of HTE library results. A. comparison of Zn powder vs. Zn@ChemBeads. Yields are GC corrected against a 1,3,5-trimethoxybenzene internal standard. B. Library coverage by ligand class. C. Library coverage by aryl bromide core. D. New chemical space accessible with L13. Yields are isolated from scaled up reactions after observing a hit on HTE screens.^[a] Isolated yield on 0.1 mmol scale using ChemBeads.^[b] Isolated on 0.5 mmol scale using Zn powder and stir bars.

beyond 46%. A major breakthrough was achieved when we examined non-optimal ligands derived from our Pfizer collaboration.^[5a] We found that the ligand bipyridine-6-carboxamidine (BpyCam, L13) proved to be general and, in some cases, complementary to dtbbpy and PyBCam^{CN} (Scheme 2B and D).

The success of L13 was surprising because, while pyridine carboxamidines and pyridine bis(carboxamidine) ligands have proven to be useful in several cross-coupling reactions,^[5a,10d,22b] the value of (BpyCam)NiCl₂ was only evident when tested against a diverse, challenging library. In analogy to similar situations in biology, we term this a “cryptic” catalyst.^[30]

The overall hit rate for the 222-member μmol-scale library with the addition of L13 rose from 46% to 56% (124/222 product ions detected) (Schemes 1 and 2B). This hit rate is higher than what we had found previously using micro stir bars and a less diverse substrate set,^[13] suggesting that some of the improvement is due to better mixing/activation with ChemBeads. This number is also impressive when considered in context: even methods considered reliable can give moderate hit rates in diverse medicinal chemistry libraries. For example, Merck noted only 45% of metal-catalyzed C–N bond forming reactions on complex, polar substrates succeeded.^[1b] Similarly, internal AbbVie data for Pd-catalyzed amine arylation^[31] gave a 55% hit rate.

Examination of the array reveals the differences and similarities between the three catalysts. For example, reactions conducted with each ligand had a similar level of success: 79/222 (36%) for PyBCam^{CN} (L1), 61/222 (27%) for dtbbpy (L10), 62/222 (28%) for BpyCam (L13) (Scheme 2B). There was also considerable heterogeneity in what substrate combinations were successful with each ligand. For example, reactions of Core 2 did not work at all with L1, but L13 had a reasonable hit rate. On the other hand, L13 was a poor choice for Core 6, but reactions with L1 worked well. Finally, we note that the hit rate of this approach could be further improved by the use of additional modified conditions to accommodate the alkyl bromides in this study that provided no product (e.g., for adamantyl bromide,^[24,32] 2,2,2-trifluoroethyl bromide,^[33] MOM–Br,^[34] and 1-(2-bromoethyl)-2-methylpyrrolidine^[35]). These alkyl coupling partners accounted for 24% of the reactions that failed to show any product in HTE screening. The use of even ten different sets of conditions is routine and not a barrier in HTE approaches.

Cross-couplings conducted at 10 μmol scale translated to larger scale (10× and 50× scale) as well as a normal vial/stir bar format. A subset of these reactions were performed at 100 μmol scale followed by mass-directed purification resulted in the isolation of 72/124 products with >95% purity and an additional 14 products with <95% purity. The other 37 products were not isolated because the reactions had low conversion and/or isolation was hindered by overlapping peaks. We further scaled three reactions to 500 μM scale using standard lab techniques (4 mL vials with stirbars, isolations by standard flash chromatography (19, 130, 139)). Of the 87 isolated products, 27 products were fully characterized (see Supporting Information for additional details). As the main purpose of this study was to

obtain a global overview of currently accessible scope, we did not focus on reaction optimization. In our study, the reactions were carried out in parallel, with fixed concentration, temperature and reaction time, and purification was optimized for purity and speed over yield. Further optimization would presumably improve on these yields, as would the inclusion of additional conditions for specialized substrates.

These results demonstrate the power of using μmol scale high throughput experimentation to quickly identify workable conditions and map out the reactivity space of the substrates of interest. The sensitivity of the analysis tool (UPLC-MS) ensured even a trace amount of product peak signal could be detected, thus greatly eliminating the possibility for false negative findings on the micromole scale. *This workflow, which is accessible with a minimal investment, allows researchers to get a global understanding of gaps in scope while using minimal amounts of material (for 666 reactions, 1.11 mmol of each core, 0.36 mmol of each alkyl halide, and 0.16 mmol of each ligand) and time (the screens were conducted over about two weeks).*

We anticipate that the use of Zn@ChemBeads for cross-electrophile coupling will be broadly useful in HTE. Indeed, based on this study and the promising results we obtained, this methodology has become one of the few methods we use in screening aryl-alkyl coupling conditions for complex med-chem substrates. In addition, this study suggests that HTE libraries could be used to find catalysts that are general, but whose value is not evident with relatively simple substrate pairs. A corollary to this suggestion is that collections of ligands should be focused on diversity as much as performance in one or two test reactions. Ligands that might appear to be poor choices, and are thus not routinely screened, might in fact be just as useful as optimal ligands. These “cryptic catalysts” only show their value when challenged with the correct prompts, a task that is now possible with modern HTE.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: nickel · cross-electrophile coupling · high-throughput experimentation · medicinal chemistry · carbon-carbon bond formation

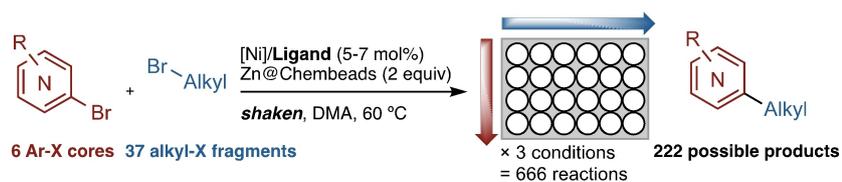
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discovery of a new, useful catalyst. Although the reactions are heterogeneous, the glass beads enable the use of shakers instead of complex micro stirrers.

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ChemBead Enabled High-Throughput Cross-Electrophile Coupling Reveals a New Complementary Ligand

