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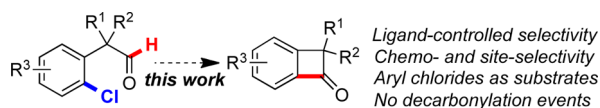
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ABSTRACT



The first Pd-catalyzed intramolecular acylation of aryl chlorides via C–H bond functionalization is presented. The method allows for the synthesis of a variety of elusive benzocyclobutenones with a wide range of functional groups and substitution patterns. We demonstrate that a change in the ligand backbone dictates the selectivity pattern.

Metal-catalyzed C–H arylation protocols are now widely recognized as powerful synthetic tools in organic synthesis.¹ Despite the utility of aldehydes, perhaps the most versatile synthon in organic synthesis, an arylation event via C–H functionalization of the aldehyde motif, is underrepresented in the C–H arylation arena.² A close survey of the existing methodologies shows that directing groups are generally required and that the control of selectivity still represents a major concern;^{2,3} however, the cleavage of directing groups is notoriously difficult under mild reaction conditions, thus limiting the application profile of these methodologies and enforcing a change in strategy. In this regard, the use of aryl halides constitutes an excellent alternative for increasing

molecular complexity while lowering the overall cost for producing fine chemicals.⁴

In order to demonstrate the potential of the intramolecular acylation techniques via C–H functionalization, we envisioned the synthesis of benzocyclobutenones (BCBs), unique scaffolds with great significance due to their versatility as synthetic intermediates.⁵ Such logic unravels readily accessible α -aryl aldehydes⁶ as the key building blocks (Scheme 1). This transformation is quite remarkable, as one C–C bond must be formed while generating a rather strained ring. Recently, we reported the preparation of BCBs via C–H functionalization with aryl bromides as coupling counterparts.⁷ Unfortunately, this protocol was not yet satisfactory, since (a) the less reactive and more accessible aryl chlorides were totally inert;⁴ (b) the method showed low selectivity with multiple reaction sites, and (c) the reaction was restricted to α,α -disubstituted benzocyclobutenones. Although one might anticipate that

(1) For selected reviews: (a) Yeung, C. S.; Dong, M. V. *Chem. Rev.* **2011**, *111*, 1215. (b) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. (c) McMurray, L.; O'Hara, F. O.; Gaunt, M. *Chem. Soc. Rev.* **2011**, *40*, 1885. (d) Lyons, T. W.; Sanford, M. *Chem. Rev.* **2010**, *110*, 1147. (e) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (f) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

(2) For reviews in C–H hydroacylation using alkynes or alkenes as coupling partners: (a) Leung, J. C.; Krische, M. J. *Chem. Sci.* **2012**, *3*, 2202. (b) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725.

(3) For selected references: (a) Li, C.; Wang, L.; Li, P.; Zhou, W. *Chem.—Eur. J.* **2011**, *17*, 10208. (b) Tang, B.; Song, R.; Wu, C.; Liu, Y.; Zhou, M.; Wei, W.; Deng, G.; Yin, D.; Li, J.-H. *J. Am. Chem. Soc.* **2010**, *132*, 8900. (c) Baslé, O.; Bidange, J.; Shuai, Q.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 1145. (d) Sangwon, K.; Byungman, K.; Chang, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 455. (e) Satoh, T.; Itaya, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1996**, 823.

(4) *Metal-catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.

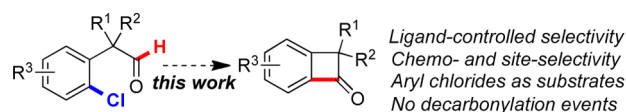
(5) For selected references: (a) Takahashi, N.; Kanayama, T.; Okuyama, K.; Kataoka, H.; Fukaya, H.; Suzuki, K.; Matsumoto, T. *Chem.—Asian. J.* **2011**, *6*, 1752. (b) Mori, K.; Ohmori, K.; Suzuki, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 5633. (c) Hamura, T.; Suzuki, T.; Matsumoto, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 6294. (d) Ohmori, K.; Mori, K.; Ishikawa, Y.; Tsuruta, H.; Kuwahara, S.; Harada, N.; Suzuki, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 3167. (e) Hosoya, T.; Kuriyama, Y.; Suzuki, K. *Synlett* **1995**, 635.

(6) (a) Martin, R.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 4561. (b) Vo, G. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2127. (c) Martin, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236.

(7) Álvarez-Bercedo, P.; Flores-Gaspar, A.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 466.

Heck-type processes could also be utilized for similar purposes,⁸ the inherent rigidity of the four-membered ring makes such a scenario highly unlikely.⁹ Despite the simple structure of BCBs, the drawbacks imparted by classical methods in terms of functional group tolerance and substitution patterns¹⁰ contribute to the perception that our approach in Scheme 1 represents a straightforward alternative to these compounds. Herein, we describe the first successful intramolecular acylation of aryl chlorides via C–H functionalization as a means to access BCBs that are beyond reach otherwise. In addition to the preparative aspects, our results reveal exquisite selectivity control depending on the chosen ligand.

Scheme 1. Synthetic Approach to BCBs Using Aryl Chlorides



We began our study with **1a** as the model substrate (Scheme 2). On the basis of our own findings,¹¹ we anticipated that the supporting ligand would play an important, if not crucial, role in the route to **2a**. Among all the ligands examined, N-heterocyclic carbenes (NHCs), showed superior activity as compared to phosphine ligands.¹² It is noteworthy that, unlike other aldehyde C–H functionalization reactions,² competitive decarbonylation of **1a** was not observed in the crude reaction mixtures. Intriguingly, while **L1** afforded **3a** exclusively, the presence of a bulky adamantyl group in **L2** had a deleterious impact on selectivity, with **2a** in a 1:2 ratio (**2a:3a**). Gratifyingly, we found that **L3**, readily available on large scale from cheap commercial sources,¹⁴ produced **2a** as the only product, albeit in lower yields. Other related NHCs such as **L4–L6** afforded mixtures of both **2a** and **3a**, thus showing the subtleties of the catalytic system.¹⁵

(8) For Heck-type acylation approaches using aryl halides not involving C–H bond-activation protocols, see: (a) Colbon, P.; Ruan, J.; Purdie, M.; Xiao, J. *Org. Lett.* **2010**, *12*, 3670. (b) Ruan, J.; Saidi, O.; Iggo, J. A.; Xiao, J. *J. Am. Chem. Soc.* **2009**, *130*, 10510.

(9) The double bond in the enamine intermediate is not flexible enough to bend in the proper conformation for the Heck coupling: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

(10) For selected references: (a) Hamura, T.; Ibusuki, Y.; Sato, K.; Matsumoto, T.; Osamura, Y.; Suzuki, K. *Org. Lett.* **2003**, *5*, 3551. (b) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Matsumoto, T.; Suzuki, K. *Synlett* **1995**, 177. (c) Aidhen, I. S.; Ahuja, J. R. *Tetrahedron Lett.* **1992**, *33*, 5431.

(11) (a) Ziadi, A.; Martin, R. *Org. Lett.* **2012**, *14*, 1266. (b) Barbero, N.; Martin, R. *Org. Lett.* **2012**, *14*, 796. (c) Novák, P.; Correa, A.; Gallardo-Donaire, J.; Martin, R. *Angew. Chem.* **2011**, *123*, 12444. (d) Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2009**, *131*, 15974.

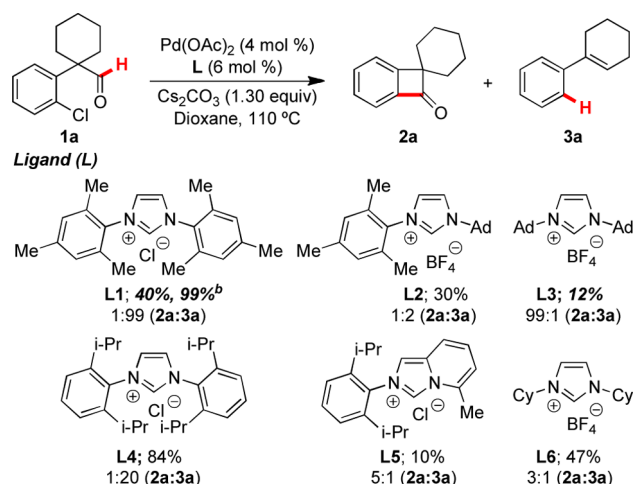
(12) For recent reviews, see: (a) Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6940. (b) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768.

(13) For a related transformation using aryl bromides as substrates: Flores-Gaspar, A.; Martin, R. *Adv. Synth. Catal.* **2011**, *353*, 1222.

(14) Richter, H.; Schwertfeger, H.; Schreiner, P. R.; Fröhlich, R.; Glorius, F. *Synlett* **2009**, 193.

(15) For the use of other NHC ligands, see Supporting Information.

Scheme 2. Striking NHC Effects on Selectivity^a



^a GC yields using dodecane as internal standard. ^b Using **5** (2 mol %).

The observed selectivity switch by catalyst tuning allows us to distinguish between different mechanistic scenarios.¹⁶ At present, we suggest that the higher buried volume of **L3** is critical for achieving selectivity.^{17,18} Subsequently, the effects of palladium precatalysts, solvents, bases, and temperatures were systematically examined (Table 1). While typically employed Pd(OAc)₂ resulted in lower yields (entry 1), the use of allyl chloride palladium dimers **5–6** gave better results (entries 3–4), with a catalyst based upon **5** being the most active (entry 5). At this stage, we hypothesized that the presence of additives could accelerate the C–H functionalization event; as shown in entries 8–12, this was indeed the case. After some optimization, we found that the synergistic use of **L3** and allyl ether (**9**) allowed for the preparation of **2a** in 80% yield (entry 10). We currently support the notion that allyl ether might be crucial for stabilizing monoligated **L3**–Pd(0) species.^{19,20}

Next, we set out to explore the preparative scope of this reaction. As shown in Scheme 3, the functional group tolerance is nicely illustrated by the fact that differently substituted silyl ethers (**2d** and **2e**), alkenes (**2g**), esters (**2l**), aldehydes (**2m** and **2q**), ketones (**2n**), nitriles (**2p**), amines (**2o** and **2r**), fluorides (**2t**), or heterocycles (**2s**) are perfectly

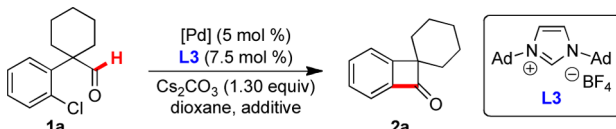
(16) For recent examples of this concept: (a) Shareet, A.-R.; Sherman, D. H.; Montgomery, J. *Chem. Sci.* **2012**, *3*, 892. (b) Kwak, J.; Kim, M.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 3780. (c) Urban, S.; Ortega, N.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 3803. (d) Malik, H. A.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2010**, *132*, 6304.

(17) (a) Hillier, A. C.; Sommer, W. J.; Yong, B. S.; Petersen, J. L.; Cavallo, L.; Nolan, S. P. *Organometallics* **2003**, *22*, 4322. (b) Dorta, R.; Stevens, E. D.; Scott, N. M.; Costabile, C.; Cavallo, L.; Hoff, C. D.; Nolan, S. P. *J. Am. Chem. Soc.* **2005**, *127*, 2485. (c) Clavier, H.; Nolan, S. P. *Chem. Commun.* **2010**, 46, 841.

(18) According to ref 12, the calculated buried volumes in Ni(CO)₃L are the following: %V_{bur}(IMes) = 26, %V_{bur}(IPr) = 29, %V_{bur}(ICy) = 23, and %V_{bur}(IAd) = 37.

(19) (a) Selvakumar, K.; Zapf, A.; Spannenberg, A.; Beller, M. *Chem.—Eur. J.* **2002**, *8*, 3901. (b) Jackstell, R.; Andreu, M. G.; Frisch, A. C.; Selvakumar, K.; Zapf, A.; Klein, H.; Spannenberg, A.; Röttger, D.; Briel, O.; Karch, R.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 986.

(20) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366.

Table 1. Optimization of Reaction Conditions^a


entry	Pd source	<i>t</i> (°C)	additive ^b	yield (%) ^a
1	Pd(OAc) ₂	110	-	12
2	4	110	-	6
3	5	110	-	34
4	6	110	-	19
5	5	140	-	60
6	5	140	-	33 ^c , 50 ^d
7	5	140	7	55
8	5	140	8	71
9	5	140	9	73
10	5^e	140	9	80
11	5^e	140	9	23 ^f
12	5^e	140	9	30 ^g

4 (R=H)

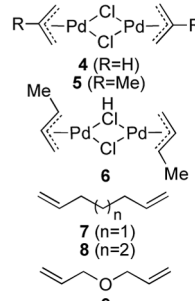
5 (R=Me)

6

7 (n=1)

8 (n=2)

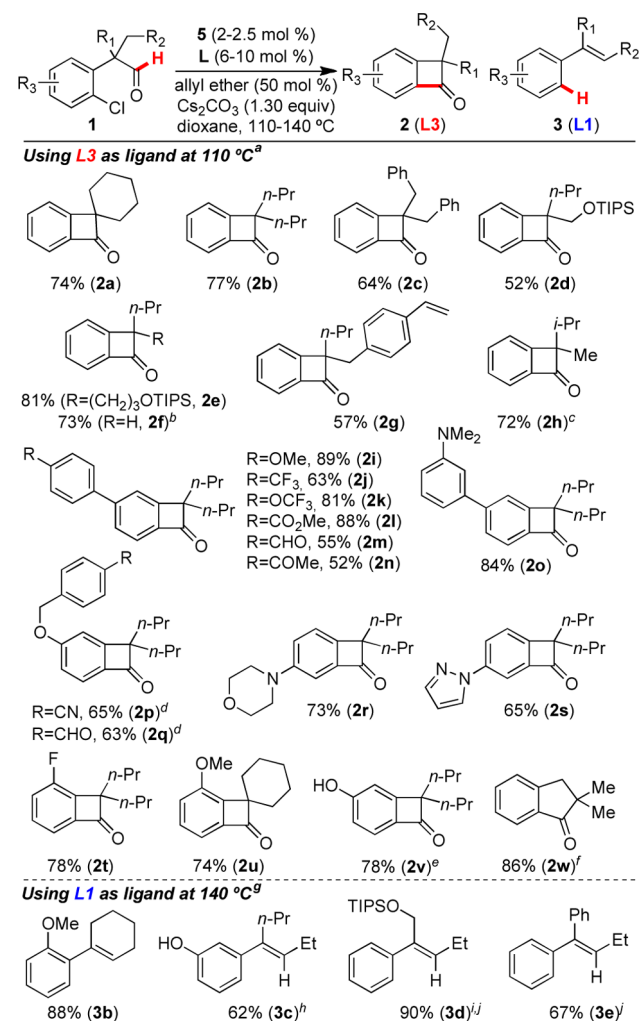
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^a **1a** (0.50 mmol), Pd (5 mol %), **L3** (7.5 mol %), Cs₂CO₃ (1.30 equiv), dioxane (0.25 M); GC yield using dodecane as internal standard. ^b 50 mol %. ^c THF as solvent. ^d Cyclopentylmethyl ether as solvent. ^e Pd/**L3** = 1:2. ^f K₂CO₃ (1.30 equiv). ^g NaOtBuO (1.30 equiv).

accommodated, thus providing an additional handle for further manipulation. The successful preparation of **2s** indicates that the Pd catalytic species are not deactivated by the presence of strong nitrogen donors. Likewise, even unprotected alcohols (**2v**) could be coupled in good yields as well. As shown for **2t** and **2u**, *ortho*-substitution did not hinder the reaction at all. Even more important is the fact that this method allows, for the first time, the preparation of a monosubstituted BCB (**2f**) when using α -silylated aryl aldehydes as precursors. This is particularly noteworthy in view of the inability of aryl bromides to promote an otherwise identical reaction.^{7,21} In striking contrast to the previous use of aryl bromides,⁷ the method could also be extended to the preparation of five-membered rings (**2w**). Notably, no competing intermolecular acylation events were detected by spectroscopy of the crude reaction mixtures, thus selectively obtaining **2m** and **2q**. Overall, we believe these results not only show the exceptional activity and functional group compatibility but also the robustness of C–H functionalization catalysts based on **L3**.²² Encouraged by the selectivity switch in Scheme 2 when utilizing **L1**, a further extension of the scope of styrene derivatives was envisaged. As shown in Scheme 4 (bottom), the protocol based on **L1** allows for the preparation of trisubstituted olefins **3b**, **3c**, **3d**, and **3e** with total regiocontrol and diastereoselectivities up to 8.4:1, even in the presence of free alcohols (**3c**).

The proven flexibility of this method suggested that our intramolecular C–H acylation event should be applicable to site-selectivity approaches.²³ Gratifyingly, substrates

Scheme 3. Reaction Scope

^a As for Table 1 (entry 10); isolated yields, average of two independent runs. ^b The 2-(trimethylsilyl)pentanal derivative was used followed by TBAF treatment. ^c Due to its volatility, the product was isolated as the benzocyclobutanone by treatment with NaBH₄ in MeOH. ^d **5** (5.0 mol %) was used. ^e Cs₂CO₃ (2.60 equiv) was used. ^f **5** (3.0 mol %), **L3** (12 mol %), allyl ether (60 mol %). ^g **5** (2 mol %) and **L1** (6.0 mol %); isolated yields. ^h E/Z = 8.4:1. ⁱ E/Z = 1:1.6. ^j 140 °C.

possessing multiple C–H or C–Cl reactive sites could be equally employed, affording **2x** and **2y** exclusively (Scheme 4); importantly, not even traces of **10** via intramolecular C–H arylation²⁴ or **11** were observed by NMR spectroscopy of the crude material.²⁵ These findings challenge the general perception that the preparation of smaller and more strained rings are lower yielding than standard routes to thermodynamically more stable medium-sized rings.

The exceptional reactivity and versatility of BCBs is illustrated in Scheme 5. Exposure of **2b** to NaBH₄ followed

(21) No monosubstituted benzocyclobutenones were obtained under the reaction conditions reported in ref 7.

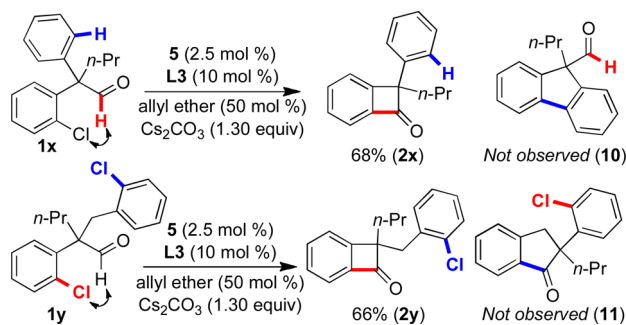
(22) The protocol based upon **L3** could also be utilized with similar yields when utilizing aryl bromides as substrates (ref 7).

(23) For a review on site selectivity in C–H bond functionalization: Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936.

(24) For selected examples of C–H intramolecular arylation with aryl chlorides, see: (a) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015. (b) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.

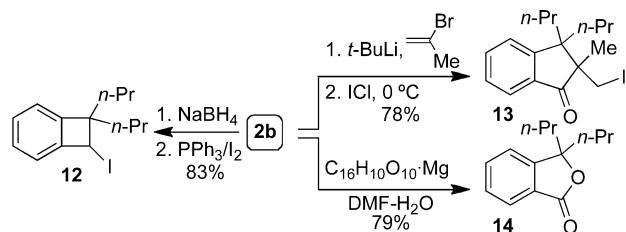
(25) Trace amounts of dechlorinated **2y** were observed in the crude reaction mixture by GC-MS.

Scheme 4. Site Selectivity with Multiple Reaction Sites



by PPh_3/I_2 treatment cleanly afforded synthetically attractive **12** in high overall yield. Likewise, indanone **13** possessing two contiguous quaternary centers or phthalide **14** could easily be obtained via ring expansion promoted by ICl^{5c} or regioselective Baeyer–Villiger oxidation with magnesium monoporphthalate.^{5e}

Scheme 5. Synthetic Applicability

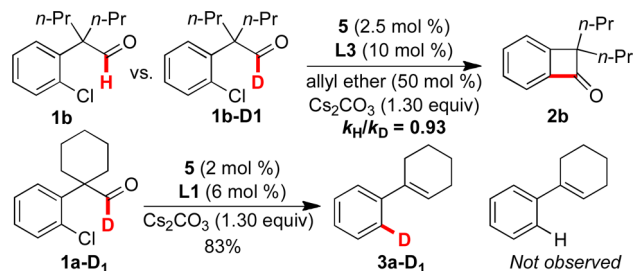


In order to gain more insight into the mechanism, we decided to gather indirect evidence via isotope labeling (Scheme 6). We observed $k_{\text{H}}/k_{\text{D}} = 0.93$ when comparing the initial rates of **1b** and **1b-D₁**. This experiment suggests that C–H cleavage is not rate determining, an intriguing

(26) (a) Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010**, *132*, 10706. (b) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157. (c) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

(27) We cannot rule out a mechanism consisting of an addition of the C–Pd bond across the C=O bond. For selected insertions of Pd oxidative addition complexes across the C=O bond, see: (a) Solé, D.; Fernández, I.; Sierra, M. A. *Chem.–Eur. J.* **2012**, *18*, 6950. (b) Fernández, I.; Solé, D.; Sierra, M. A. *J. Org. Chem.* **2011**, *76*, 1592. (c) Quan, L. G.; Lamrani, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4827.

Scheme 6. Mechanistic Studies



observation given the known literature data for related processes.^{3b,7} Quite illustrative, the deuterium label in **1a-D₁** was totally transferred to the aromatic motif in **3a-D₁** using **L1** as the ligand. At present, we support a mechanistic scenario in which the initial oxidative addition species undergoes a C–H functionalization via a concerted metalation deprotonation pathway (CMD)²⁶ and, in the presence of **L3**, final reductive elimination to afford the desired BCB **2** while recovering the active species.^{7,27} We propose that the less-sterically encumbered **L1** facilitates an intramolecular proton transfer followed by CO extrusion and β -hydride elimination, thus affording the olefin **3**.¹³

In summary, the first intramolecular acylation of aryl chlorides via C–H bond functionalization en route to benzocyclobutenones has been developed. The protocol is characterized by its broad scope and exceptional site selectivity in which *the ligand backbone dictates the selectivity pattern*. We believe such a transformation will bring new knowledge in catalyst design. In further studies, we aim to explore the asymmetric reaction and the potential of this and related transformations.

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Supporting Information Available. General procedures and spectral data for all new compounds (**2a–2y**, **3a–3f**, and **12–14**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.