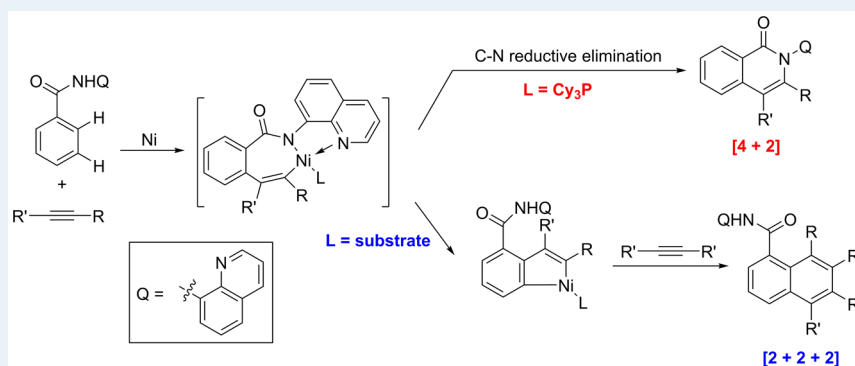


## Diverting C–H Annulation Pathways: Nickel-Catalyzed Dehydrogenative Homologation of Aromatic Amides

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## Supporting Information



**ABSTRACT:** Direct homologation of aromatic amides with internal alkynes has been accomplished via a nickel-catalyzed sequential C–H activation reaction. The use of a rigid chelating group and a strong aprotic polar solvent successfully divert the classical [4 + 2] annulation to the [2 + 2 + 2] homologation pathway. This transformation is promoted by a simple nickel catalyst without the need of stoichiometric metal oxidants. Mechanistic studies support an unusual substrate-assisted ligand exchange process. NMR and X-ray data suggest a [5,5] Ni-bridged metallacycle as the catalyst resting state. Substrate assisted directing group swap plays an important role for the subsequent *meta*-C–H insertion. In contrast, [4 + 2] annulation can be accomplished using a bulky, electron-rich phosphine ligand, which favors rapid reductive C–N elimination.

**KEYWORDS:** nickel catalysis, C–H activation, dehydrogenative homologation, phosphine, directing group

## INTRODUCTION

Nickel-catalyzed reactions have rapidly advanced over the past decade.<sup>1</sup> This abundant and cheap first-row transition metal is shown capable of promoting many valuable, yet challenging cross-coupling reactions involving secondary and tertiary alkyl halides, ethers, and phenol derivatives, which distinguish Ni from second and third row d<sup>10</sup> transition metals.<sup>2</sup> Recently, Nickel-catalyzed direct functionalization of inert C–H bonds also enjoyed rapid evolution. Early reports primarily dealt with reactions involving Ni insertion into acidic C–H bonds, such as azoles, perfluorobenzenes, and pyridine derivatives.<sup>3</sup> Subsequent studies revealed that Ni(II) can insert into electronically unbiased sp<sup>2</sup> or sp<sup>3</sup> C–H bonds selectively with the help of a bidentate directing group (DG) and phosphine ligands.<sup>4</sup> In 2011, Chatani and co-workers reported the first Ni-catalyzed [4 + 2] C–H annulation of arenes and alkynes via chelation control.<sup>4d</sup> In 2013, directed *ortho*-alkylation of benzamides via Ni(II) catalysis was reported by the same group.<sup>4e</sup> It is believed that a strong, bidentate directing group is essential for the rate-limiting C–H nickelation step, which generally requires higher temperature than Pd catalyzed processes.<sup>5</sup> Recently, C–C bond formation via sp<sup>3</sup> C–H activation were reported by Chatani and Ge groups independently.<sup>4g,j,k,m</sup> Although these pioneering work demonstrated the feasibility of

nickel to activate and functionalize an inert C–H bond, the types of new bond formation remain scarce compared to the more mature Pd and Rh catalysis.<sup>6</sup> For example, reaction involving multiple C–H activation remains challenging for this unique and intriguing metal.<sup>4a,h</sup>

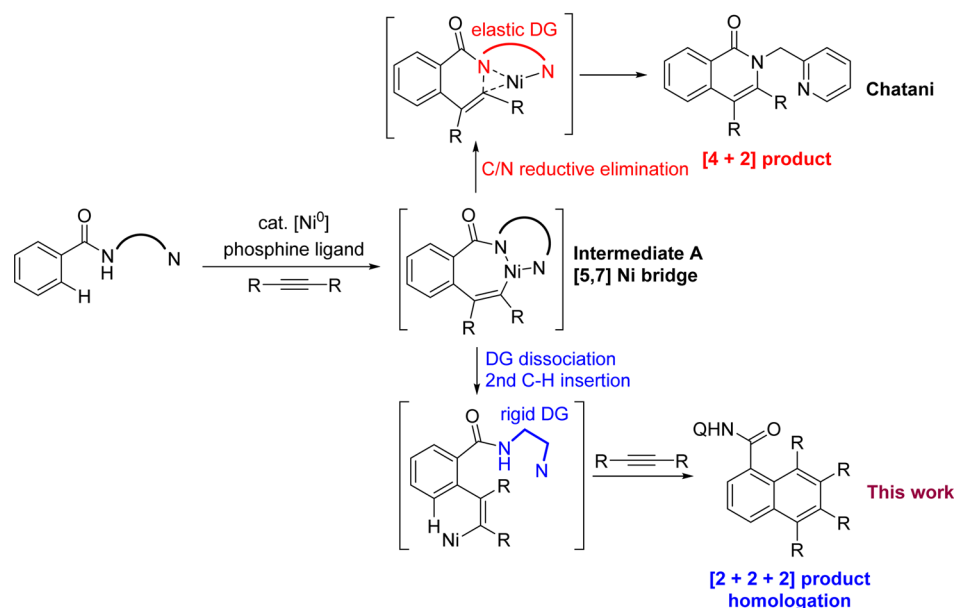
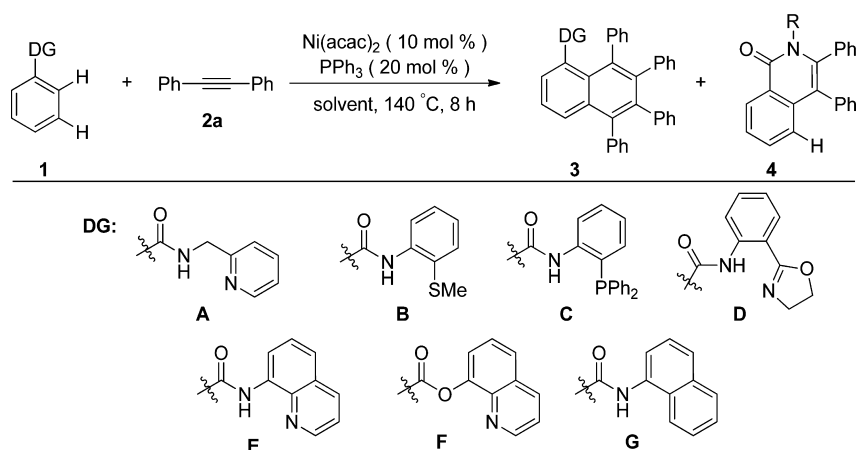
Recently, polycyclic aromatic hydrocarbons (PAHs) have attracted much attention due to their unique electro- and photochemical properties as organic semiconductors and luminescent materials.<sup>7</sup> Various synthetic methods have been developed to access this particular chemical space.<sup>8</sup> Arguably, transition-metal-catalyzed [2 + 2 + 2]-type aromatic homologation by C–H activation is an efficient and modular strategy to extend aromaticity of arenes.<sup>9</sup> In 2008, Miura and Satoh first reported a Rh(III)-catalyzed oxidative annulation reaction using phenylazoles or 2-phenylpyridine and diarylacetylenes via double C–H activation that avoids preactivation of the aryl C–Hs.<sup>10</sup> In 2008, Wu and co-worker reported Pd(II) catalyzed homologation of benzene derivatives.<sup>11</sup> Cramer and co-workers developed a Rh(III)-catalyzed homologation reaction of naphthalenes and related compounds.<sup>12</sup> The oxidative nature of this chemistry

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## Scheme 1. Two Reaction Pathways of Ni-Catalyzed C–H Annulation Reactions Involving Alkynes

## Nickel catalyzed C-H/alkyne annulation

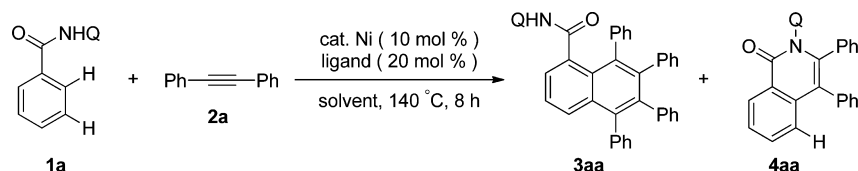
Table 1. Impact of Solvent and Directing Group on the [2 + 2 + 2] Pathway<sup>a</sup>

entry	DG	solvent	yield (%) <sup>b</sup>	3:4 <sup>b</sup>
1	A	DMA	8	0:100
2	B	DMA	0	
3	C	DMA	0	
4	D	DMA	58	2.6:1
5	E	DMA	78	6.8:1
6	F	DMA	0	
7	G	DMA	0	
8	E	toluene	10	1:1
9	E	DMSO	32	7:1
10	E	DMF	15	6.5:1
11	E	NMP	85	6.7:1
12	E	DMPU	93	6.2:1

<sup>a</sup>Reactions were conducted using 0.125 mmol **1**, 0.5 mmol diphenylacetylene **2a**, 10 mol % Ni(acac)<sub>2</sub>, 20 mol % PPh<sub>3</sub> in 1 mL solvent under Ar at 140 °C for 8 h. <sup>b</sup>Determined by <sup>1</sup>H NMR integration against 1,3,5-trimethoxybenzene as the external standard.

demands stoichiometric amounts of external oxidants, such as copper and silver salts, to turn over the metal catalyst. This limitation becomes increasingly burdensome for large scale production and substrates sensitive to oxidants. In contrast,

[2 + 2 + 2] annulation using cheap Ni or Fe catalysts has been scarce,<sup>4u,8i,13</sup> due to the predominant [4 + 2] reaction pathway. In this article, we report our recent mechanistic findings that led to precise control of these cyclization pathways.

Table 2. Impact of Ligand and Catalyst on the [2 + 2 + 2] C–H Annulation<sup>a</sup>

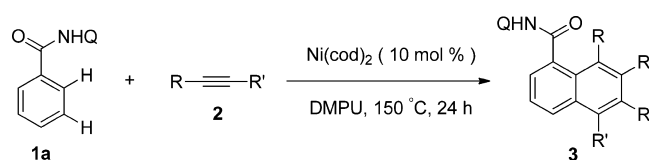
entry	Ni source	ligand	yield (%) <sup>b</sup>	3:4 <sup>b</sup>
1	Ni(acac) <sub>2</sub>	PPh <sub>3</sub>	93	6.2:1
2	Ni(acac) <sub>2</sub>	P(4-MeC <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	97	5.1:1
3	Ni(acac) <sub>2</sub>	P(4-MeOC <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	86	4.1:1
4	Ni(acac) <sub>2</sub>	P(4-FC <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	96	7.0:1
5	Ni(acac) <sub>2</sub>	P(4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	80	15:1
6	Ni(acac) <sub>2</sub>	none	70	>20:1
7 <sup>c</sup>	Ni(OTf) <sub>2</sub>	none	28	>20:1
8	NiCl <sub>2</sub>	none	31	>20:1
9	Ni(cod) <sub>2</sub>	none	95 (92)	>20:1

<sup>a</sup>Reactions were conducted using 0.125 mmol **1a**, 0.5 mmol diphenylacetylene **2a**, 10 mol % Ni catalyst, 20 mol % ligand in 1 mL solvent under Ar at 140 °C for 8 h. <sup>b</sup>Determined by <sup>1</sup>H NMR integration against 1,3,5-trimethoxybenzene as the external standard. The number in parentheses is the isolated yield. <sup>c</sup>The reaction was carried out for 48 h. Q = 8-aminoquinolinyl.

## RESULTS AND DISCUSSION

Reports by Matsubara,<sup>14</sup> Murakami,<sup>15</sup> Cheng,<sup>16</sup> and Chatani<sup>4d</sup> demonstrated that Ni catalyzed arene-alkyne annulation reactions proceed via a [4 + 2] pathway due to facile C/N reductive elimination from a Ni(II) center. Isoquinolones were exclusively obtained. This C–N bond formation requires compression of the C–Ni–N bond angle of intermediate A in order to pull the carbon and nitrogen atoms together (Scheme 1). Consequently, the N–Ni–N bond angle needs to expand to accommodate this conformational change. This calls for N,N-chelating groups with stretchable bite angles. In Chatani's case, 2-pyridinylmethylamine was found as a good DG for this purpose. In order to divert the [4 + 2] annulation to the [2 + 2 + 2] homologation pathway, we envisioned a more rigid DG would prohibit significant bite angle change and disfavor C–N bond formation leading to the [4 + 2] product. In addition, a rigid DG would dissociate more readily from the strained [5,7] Ni bridge (intermediate A), setting stage for bond rotation and second C–H insertion. This design echoes a recent report by Chatani using the similar rigid DG strategy.<sup>4u</sup> Considering reductive elimination is more difficult for electron-rich metal centers, we also proposed using an electron-rich phosphine ligand or solvent to further discourage the C–N bond formation.

**Impact of Solvent and Directing Group.** To verify this proposal, we first examined benzamide/alkyne annulation reactions using various DGs in DMA (Table 1). Phosphine ligand was used to facilitate C–H metalation as suggested by previous reports on Ni catalyzed C–H activation reactions.<sup>3,4</sup> As expected, 2-pyridinylmethylamine substrate (Table 1, DG A, Chatani's substrate for the [4 + 2] annulation) resulted the [4 + 2] product exclusively. No [2 + 2 + 2] product was observed. The low yield (8%) was likely attributed polar solvent DMA, which might serve as an ligand and increase the electron density of Ni(II). The starting material decomposed when 2-(methylthio)aniline was used as the DG (B), due to poor stability of the C–S bond under the reaction condition. The use of 2-(diphenylphosphino)aniline as DG (C) resulted in no reaction, suggesting a N,N-chelating DG is essential for C–H insertion. Interestingly, *ortho*-dihydrooxazolyl aniline (D) was found to be a competent DG. A mixture of [2 + 2 + 2] and [4 + 2] products were obtained (42% vs 16%). Improved yield and selectivity was

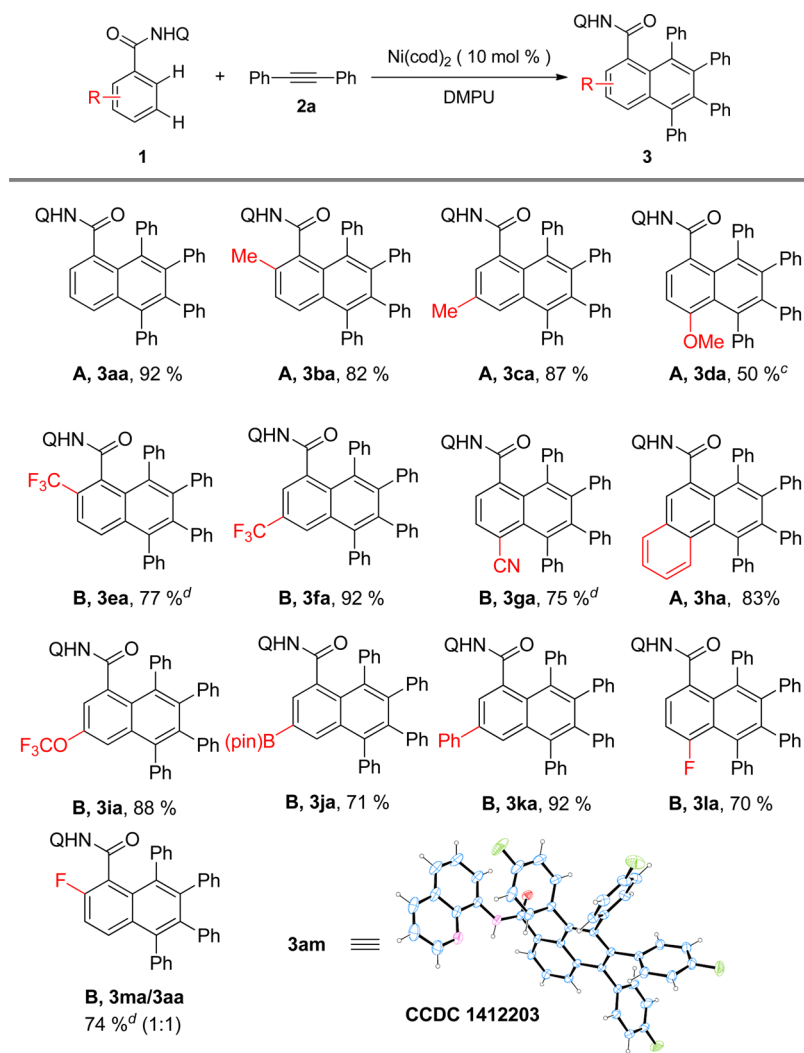
Table 3. Substrate Scope for Internal Alkyne<sup>a,b</sup>

entry	R	R'	product	yield (%) <sup>b</sup>
1 <sup>c</sup>	<i>n</i> Bu	<i>n</i> Bu	3ab	63
2 <sup>c</sup>	<i>n</i> Pr	<i>n</i> Pr	3ac	53
3 <sup>c</sup>	Me	Ph	3ad	57
4 <sup>c</sup>	<i>n</i> Bu	Ph	3ae	60
5 <sup>c</sup>	4-MeOPh	4-MeOPh	3af	66
6	4-CF <sub>3</sub> -Ph	4-CF <sub>3</sub> -Ph	3ag	77
7	4-MeS-Ph	4-MeS-Ph	3ah	57
8	4-Me-Ph	4-Me-Ph	3ai	81
9	4-CN-Ph	4-CN-Ph	3aj	70
10	2-thiophenyl	2-thiophenyl	3ak	69
11 <sup>d</sup>	4-MeOPh	4-CN-Ph	3al	67 <sup>d</sup>
12	4-F-Ph	4-F-Ph	3am	86

<sup>a</sup>Reaction condition: amide (0.125 mmol), alkyne (0.5 mmol), Ni(cod)<sub>2</sub> (0.0125 mmol) in 0.5 mL DMPU, at 150 °C for 24 h. <sup>b</sup>Isolated yields average of two runs. <sup>c</sup>Ni(cod)<sub>2</sub> (0.025 mmol) was used and reactions were run at 160 °C. <sup>d</sup>The ratio of 4 isomers is 1:1:1.6:1.6

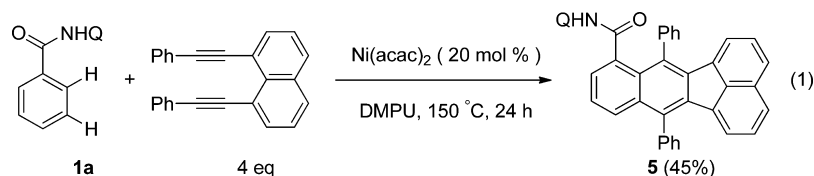
obtained by using a directing group with higher rigidity: 8-aminoquinoline (E). The desired homologation product was obtained in 78% NMR yield with moderate [2 + 2 + 2] vs [4 + 2] selectivity. The reaction did not take place for both 8-hydroxyquinoline ester (F) and *N*-2-naphthyl benzamide (G) substrates, indicating both nitrogen atoms are required. As predicted, lower ratio of [2 + 2 + 2]/[4 + 2] was observed in nonpolar solvent such as toluene. In aprotic polar solvents, the reaction afforded much higher conversions to [2 + 2 + 2] homologation product **3aa**. The best result was obtained when 8-aminoquinoline was used as DG in NMP or DMPU. The desired polysubstituted naphthalene product **3aa** was obtained 80% yield, along with 13% isoquinolone (Table 1, entry 12).

**Impact of Ligand and Catalyst.** Having identified the promising DG and solvent, we next examined the effects of the phosphine ligands and nickel catalysts. We initially expected that electron-rich phosphine ligands would increase the electron

Table 4. Substrate Scope of Arenes<sup>a,b</sup>

<sup>a</sup>Amide (0.125 mmol), alkyne (0.5 mmol), Ni(cod)<sub>2</sub> (0.0125 mmol) using (Condition A) in 1 mL DMPU, at 140 °C for 8 h, or (Condition B) in 0.5 mL DMPU, at 150 °C for 18 h. <sup>b</sup>Isolated yields average of two runs. <sup>c</sup>Run at 150 °C. <sup>d</sup>Run at 160 °C.

## Scheme 2. Homologation Using a Dialkyne Substrate

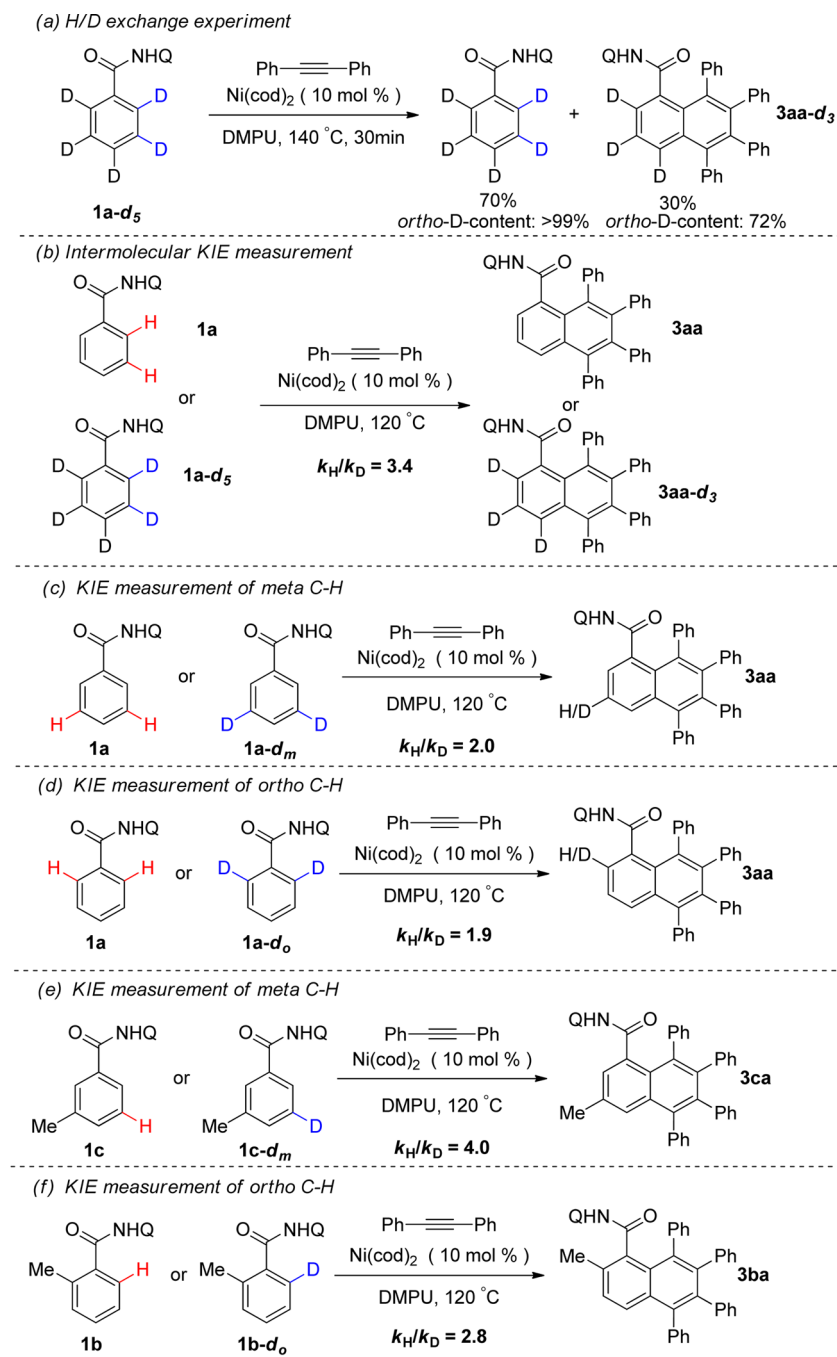


density on the nickel center of intermediate **A** (Scheme 1) and slow down the terminating C/N bond reductive elimination. In turn, it might facilitate DG disassociation from Ni and trigger the second C–H metalation. However, moderate [2 + 2 + 2]/[4 + 2] ratio (Table 2, entries 1–3, **3aa/4aa**) was observed for electron-rich triarylphosphines. On the other hand, phosphines bearing electron-withdrawing fluoro or trifluoromethyl aryls led to improved selectivity toward homologation (entry 4 and 5). Following this trend, we removed phosphine ligand from the reaction. To our delight, the [4 + 2] pathway leading to **4aa** was completely suppressed (Table 2, entry 6). We suspected this “ligand-free” reaction would be sensitive to Ni species. The use of cationic NiCl<sub>2</sub> and Ni(OTf)<sub>2</sub> resulted much lower conversions compared to Ni(acac)<sub>2</sub>. The best result was obtained using low

valent Ni(cod)<sub>2</sub>. Polysubstituted naphthalene **3aa** was obtained in 92% isolated yield. In these reactions, diphenyl acetylene serves as the terminal oxidant for the initial Ni oxidation and subsequent catalyst turnover.<sup>4d</sup> The corresponding stilbene byproduct was isolated in good yield.

**Substrate Scope for Alkyne and Aryl Amide.** With the optimized reaction condition in hand, we explored the substrate scope for both alkyne and aryl amide. Various aryl–aryl, alkyl–alkyl, and alkyl–aryl disubstituted acetylenes were tolerated. We observed serious precipitation of Ni black for dialkyl acetylenes under the standard reaction condition, indicating attenuated redox potential for these more electron-rich substrates.<sup>17</sup> Nevertheless, increasing Ni loading to 20 mol % and the reaction temperature to 160 °C was sufficient to overcome the decomposition of the

## Scheme 3. Deuterium Labeling Experiments



Ni catalyst. Moderate to good yields were obtained (Table 3, products 3ab, 3ac). For asymmetrically substituted alkyl-aryl acetylenes, a single regioisomer out of four possibilities was isolated (Table 3, product 3ad, 3ae). Interestingly, although we observed C–S bond decomposition when using DG B (Table 2), 4-MeSPh was not affected by this homologation reaction condition (Table 3, product 3ah). The reaction became complicated when acetylenes bearing two electronically different aryl groups were attempted. A mixture of regioisomers was formed.

The scope of aryl amide was studied as well (Table 4). Ortho-, meta-, and para-substituted aryls undergo the desired homologation with similar efficiency. No rate difference was observed between the sterically more hindered *o*-tolyl substrate vs its

meta-analogue (Table 4, products 3bc and 3ca). Both electron-rich and electron-poor aryl amides worked well. This reaction has a broad functional group tolerance. In particular, a B(pin) substituted benzamide substrate afforded the corresponding boron containing polynaphthalene 3ja in 71% yield which could undergo further cross-coupling reactions to introduce versatile substituents to the PAH scaffolds. Interestingly, when an *ortho*-fluoro benzamide was used, the reaction afforded a 1:1 mixture of the desired product 3ma and defluorinated product 3aa. Presumably, 8-aminoquinoline directed a C–F activation process that occurred with similar efficiency. The structures of these products were elucidated by X-ray crystallography. Substituents on the central naphthalene are all twisted out of planarity into a propellerlike conformation.

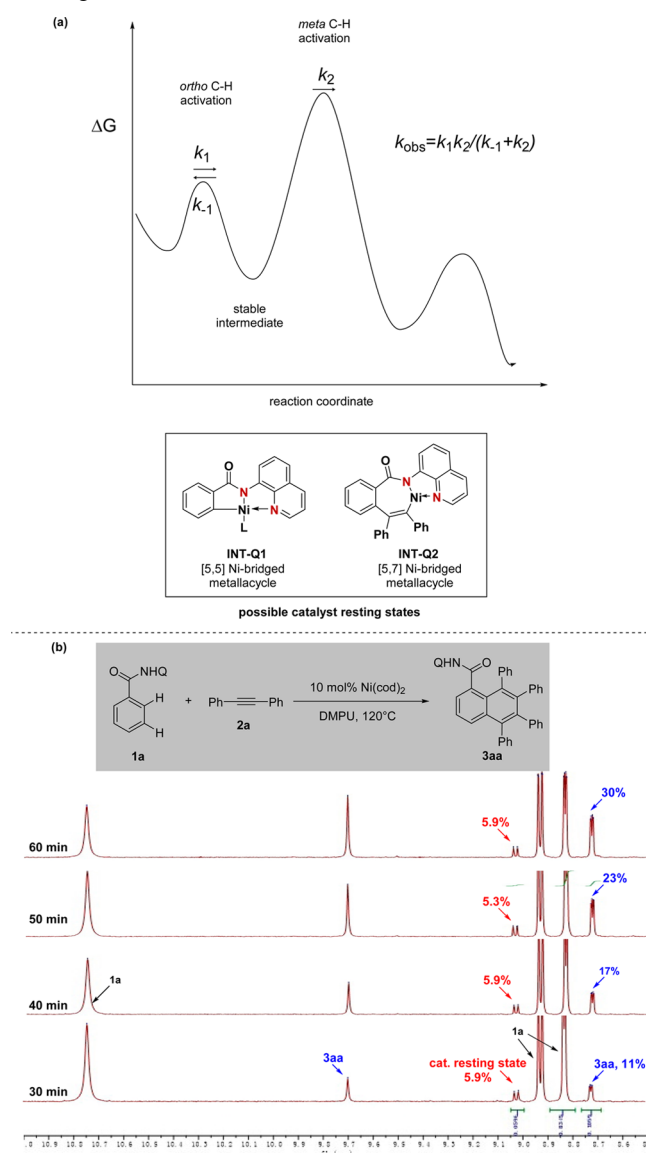
We also attempted a reaction using 1,8-bis(phenylethynyl)naphthalene as substrate. An interesting sequential annulation occurred to yield a fluoranthene product **5**, which is a popular scaffold in organoelectronic devices and fullerene chemistry (Scheme 2). This protocol provides a straightforward method to access this family of useful polyaromatic system.<sup>18</sup>

**Deuterium Labeling Experiments.** In order to probe the reaction mechanism, we carried out detailed isotope labeling experiments (Scheme 3). When *d*<sub>5</sub>-benzamide substrate was subjected to the reaction condition for a short period, the unreacted starting material was recovered without H contamination. However, 28% H incorporation was observed at the *ortho*-position of the product. This result suggests the initial N–H insertion by Ni(0) is irreversible. Hydrogen contamination in the product indicates the *ortho*-C–H metalation step might be reversible. In contrast, no H/D exchange was observed at the *meta*-positions for product **3aa-d**<sub>3</sub>. A large primary isotope effect was observed for substrate **1a-d**<sub>5</sub> (Scheme 2, b, KIE = 3.4). Smaller, yet very similar KIE values (2.0 and 1.9) were observed using *meta*- and *ortho*-deuterated substrates **1a-d**<sub>m</sub> and **1a-d**<sub>o</sub> (Scheme 2, c and d). Considering that the substrate contains two *ortho*- and two *meta*-C–Hs, we also determined the KIE values for substrates containing only one *ortho*- or one *meta*-C–H bond (Scheme 3, e and f). Again, both substrates showed significant primary isotope effect (KIE<sub>meta</sub> = 4.0, KIE<sub>ortho</sub> = 2.8). These data indicate both *ortho*- and *meta*-C–H metalation steps contribute to the overall reaction rate. The *ortho*-C–H cleavage occurs before the rate-determining step (RDS) and exhibits an equilibrium isotope effect. The *meta*-C–H activation is likely the slowest step in the catalytic cycle.<sup>19</sup> The combination of a rigid DG and a strong aprotic polar solvent contributes to both slow C/N reductive elimination and fast DG dissociation, delivering the [2 + 2 + 2] homologation product exclusively.

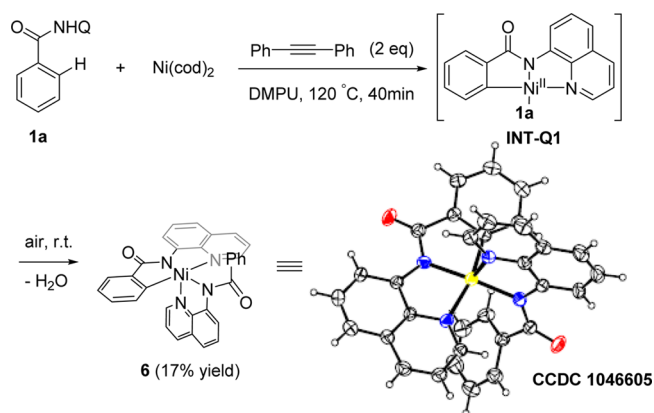
**NMR Spectroscopic Study and Isolation of Ni Complexes.** As discussed above, the *ortho*-C–H insertion is reversible. Therefore, the overall reaction carries a simplified kinetic profile illustrated in Scheme 4a. According to this analysis, there should be a stable Ni resting state between the two C–H nickelation events. In order to confirm this speculation, we followed the reaction between **1a** and **2a** at 120 °C using <sup>1</sup>H NMR. A new species was observed that remained at constant concentration (ca. 6%) throughout the course of the reaction (Scheme 4b). Upon approaching full conversion, the amount of this species started to decrease and eventually was consumed completely (see the SI). We believe this newly identified “intermediate” is likely the catalyst resting state.

The first C–H activation step involves two key Ni bridged intermediates INT-Q1 and INT-Q2 (Scheme 4a). In order to determine which one is the catalyst resting state, we attempted to isolate and determine the structure of the most stable Ni complex. The reaction of **1a** and **2a** was carried out at 120 °C using a stoichiometric amount of Ni(cod)<sub>2</sub>. The reaction was stopped after 40 min. A dark red solid was isolated. The structure of this compound was determined as a Ni(III) complex **6** (Scheme 5), which was likely a oxidation product during isolation. This result suggests that the [5,5] Ni-bridged metallacycle INT-Q1 is likely the catalyst resting state. Since the C/N reductive elimination is suppressed, the persistence of INT-Q1 implies that the corresponding [5,7] Ni-bridged metallacycle INT-Q2 is relatively unstable and DG dissociation/*meta*-C–H insertion is imminent. This argument is consistent with a condition involving a rigid DG and strong polar solvent.

**Scheme 4. Proposed Kinetic Profile and Evidence of a Catalyst Resting State**



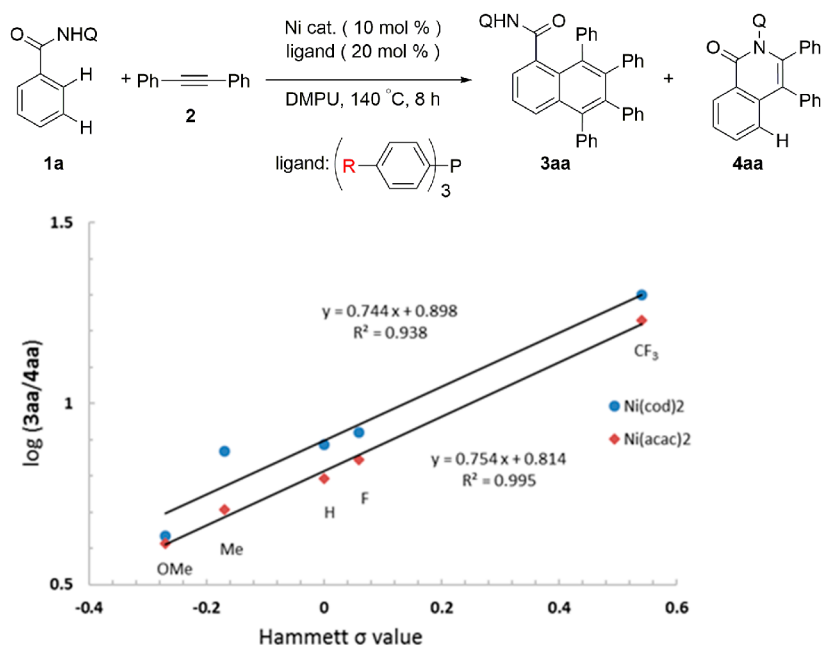
**Scheme 5. Isolation of Nickelcycle Complex**



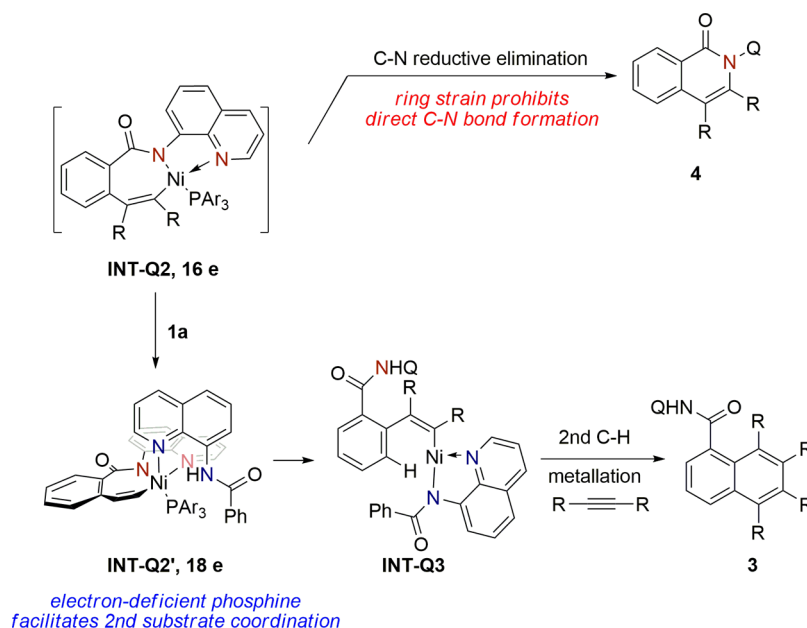
### LFER between Ligand Electronics and Selectivity.<sup>20</sup>

Intrigued by the electronic effect of phosphine ligands on the selectivity of [4 + 2] vs [2 + 2 + 2], we investigated the linear free-energy relationship (LFER) between *para*-substituted

Table 5. LFER between Ligand Electronics and Selectivity



Scheme 6. Substrate Assisted Ligand Dissociation



triarylphosphines and the ratio of  $[4 + 2]/[2 + 2 + 2]$  (Table 5). The positive slope indicates that DG dissociation/*m*-C-H metalation, compared to C/N reductive elimination, is more sensitive to the electronics of the phosphine ligand. Electron-deficient phosphines favor  $[2 + 2 + 2]$  over  $[4 + 2]$ , inspired by complex **6** structure, it likely due to decreased positive charge on the nickel by the coordination of the second substrate.

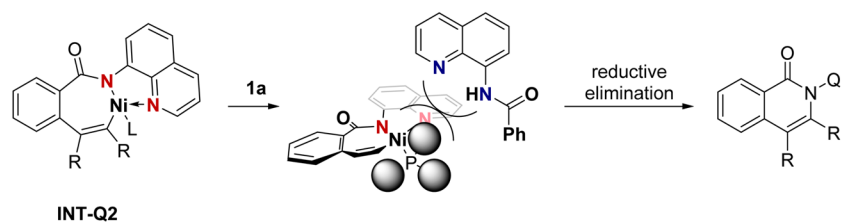
Based on this information, we propose a substrate-assisted ligand exchange pathway leading to the  $[2 + 2 + 2]$  product **3** (Scheme 6). The first alkyne insertion reaction generates intermediate INT-Q2. The rigidity of the 8-aminoquinoline ligand prohibits direct C–N bond formation from INT-Q2. INT-Q2 is a 16-electron Ni(II) complex, which is coordinated by another substrate to yield an 18-electron intermediate INT-Q2'. The increased electron density at the Ni center of INT-Q2'

triggers ligand exchange/reorganization to give INT-Q3, setting stage for the second alkyne insertion. In this process, electron-poor phosphine is a better leaving group than electron-rich ones and favors the ligand exchange.

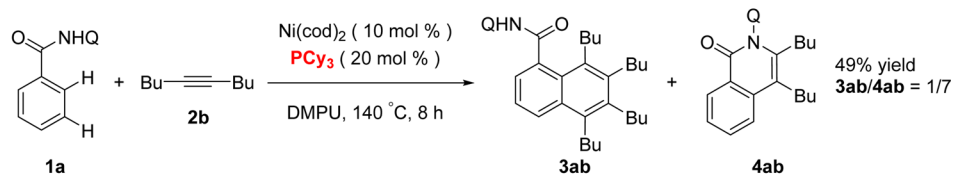
Following this analysis, we propose that a bulky electron-rich phosphine might divert the reaction pathway back to  $[4 + 2]$ . A large phosphine would discourage coordination of a second substrate molecule by creating a crowded Ni center. An electron-rich  $\text{PAr}_3$  would disfavor ligand displacement. We were pleased to find that  $\text{PCy}_3$  is an effective ligand for the  $[4 + 2]$  reaction under otherwise identical conditions. Product **4ab** was preferentially formed over **3ab** in 7:1 ratio (Scheme 7). In this reaction,  $\text{PCy}_3$  blocks second **1a** from coordinating to Ni center and the strong trans effect of this phosphine assists C/N reductive elimination by prolonging N–Ni bond. In comparison,

## Scheme 7. Diverting Reaction Pathways Using A Bulky and Electron-Rich Phosphine Ligand

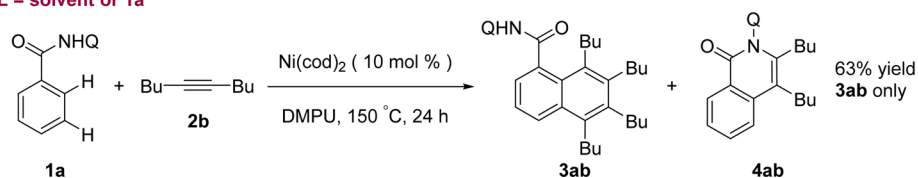
The ligand exchange process



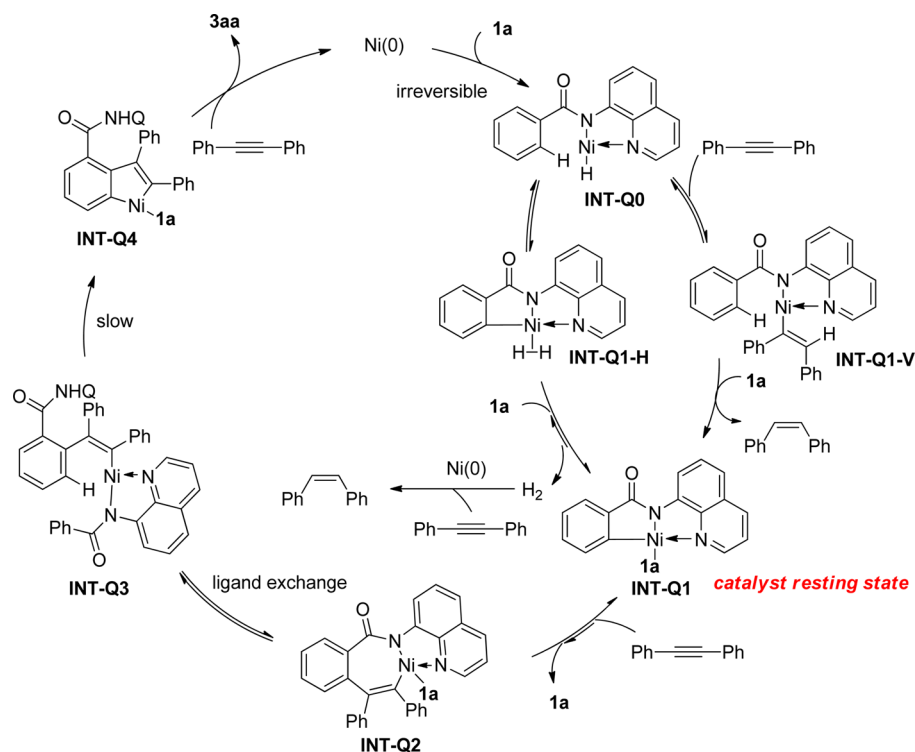
L = phosphine



L = solvent or 1a



## Scheme 8. Proposed Mechanism for the [2 + 2 + 2] Reaction Pathway



standard ligand-free condition yielded the [2 + 2 + 2] product **3ab** only.

The complete catalytic cycle for the [2 + 2 + 2] reaction is proposed in Scheme 8. Ni(cod)<sub>2</sub> is readily oxidized by the acidic amide bond to give nickel hydride INT-Q0. This oxidative addition step is likely irreversible as supported by the H/D exchange experiment (Scheme 3a). *Ortho*-C–H nickelation occurs via  $\sigma$ -bond metathesis. The H<sub>2</sub> bonded nickelacycle INT-Q1-H is consumed by alkyne to give key C–H insertion

intermediate INT-Q1, which is the catalyst resting state. Stilbene was observed in 76% by GC. Alternatively, nickelation could occur after alkyne insertion via INT-Q1-V ( $\sigma$ -bond metathesis). Fast alkyne insertion into INT-Q1 generates INT-Q2.<sup>19</sup> In the absence of an external ligand, substrate amide **1a** acts as a monodentate ligand to stabilize both INT-Q1 and INT-Q2. Intramolecular ligand exchange/DG swap gives INT-Q3. Second  $\sigma$ -bond metathesis results *meta*-C–H nickelation (INT-Q4), which is likely the slowest step. The second alkyne



insertion, followed by C–C bond reductive elimination, releases homologation product **3aa**. This mechanistic proposal also supports recent finding by the Chatani group. In their case, the same rigid 8-aminoquinoline was used as DG.<sup>4u</sup> In contrast to our ligand-free condition, a NHC ligand was used to prevent premature C–N bond reductive elimination. In their case, substrate assisted DG dissociation is unlikely to operate. As a result, higher temperature and concentrations were employed for the reaction. In addition, a close to 1 KIE value is consistent with DG dissociation being the rate-determining step.

## CONCLUSION

In summary, we developed a Ni-catalyzed dehydrogenative homologation reaction of arenes and alkynes. Polycyclic aromatic hydrocarbon scaffolds were synthesized in one step using a simple, ligand-free procedure. The common [4 + 2] reaction pathway is diverted to [2 + 2 + 2] using a rigid 8-aminoquinoline directing group. Detailed mechanistic studies suggest a substrate-assisted ligand exchange pathway leading to [2 + 2 + 2] products. A stable Ni resting state between two C–H activation events was identified experimentally. The selectivity of [2 + 2 + 2] vs [4 + 2] is influenced by both DG and ligand. A bulky, electron-rich phosphine can revert this reaction back to the [4 + 2] pathway. We expect insights gained in this endeavor will stimulate development of sophisticated C–H functionalization cascades by mechanism-inspired rationale design.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acscatal.6b02477](https://doi.org/10.1021/acscatal.6b02477).

- Experimental procedures, analytical and spectroscopic data for new compounds, copies of NMR spectra (PDF)
- Three-dimensional rotatable crystallographic information for compound **3am** (CIF)
- Three-dimensional rotatable crystallographic information for compound **6** (CIF)

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) For selected recent reviews on nickel-catalyzed reactions, see: (a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299–309. (b) Hoshimoto, Y.; Ohashi, M.; Ogoshi, S. *Acc. Chem. Res.* **2015**, *48*, 1746–1755. (c) Jackson, E. P.; Malik, H. A.; Sormunen, G. J.; Baxter, R. D.; Liu, P.; Wang, H.; Shareef, A. R.; Montgomery, J. *Acc. Chem. Res.* **2015**, *48*, 1736–1745. (d) Standley, E. A.; Tasker, S. Z.; Jensen, K. L.; Jamison, T. F. *Acc. Chem. Res.* **2015**, *48*, 1503–1514. (e) Yamaguchi, J.; Muto, K.; Itami, K. *Top. Curr. Chem.* **2016**, *374*, 55.

(2) For selected recent reviews, see: (a) Phapale, V. B.; Cárdenas, D. J. *Chem. Soc. Rev.* **2009**, *38*, 1598–1607. (b) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486–1495. (c) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417–1492. (d) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A. M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346–1416. (e) Han, F.-S. *Chem. Soc. Rev.* **2013**, *42*, 5270–5298. (f) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, 2013, 19–30.

(3) For selected examples of nickel-catalyzed activation of acidic C–H bonds, see: (a) Clement, N. D.; Cavell, K. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3845–3847. (b) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146–8147. (c) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872–8874. (d) Nakao, Y.; Kashiwara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170–16171. (e) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733–1736. (f) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737–1740. (g) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 4156–4159. (h) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 6410–6413. (i) Shirakura, M.; Sugimoto, M. *Org. Lett.* **2009**, *11*, 523–526. (j) Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12070–12071. (k) Doster, M. E.; Hatnean, J. A.; Jestic, T.; Modi, S.; Johnson, S. A. *J. Am. Chem. Soc.* **2010**, *132*, 11923–11925. (l) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2202–2205. (m) Nakao, Y.; Kashiwara, N.; Kanyiva, K. S.; Hiyama, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 4451–4454. (n) Nakao, Y.; Yamada, Y.; Kashiwara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666–13668. (o) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A. *J. Am. Chem. Soc.* **2010**, *132*, 11887–11889. (p) Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3061–3064. (q) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem. - Eur. J.* **2010**, *16*, 12307–12311. (r) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169–172. (s) Tamura, R.; Yamada, Y.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 5679–5682. (t) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 775–779. (u) Muto, K.; Yamaguchi, J.; Lei, A.; Itami, K. *J. Am. Chem. Soc.* **2013**, *135*, 16384–16387. (v) Meng, L.; Kamada, Y.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 10048–10051. (w) Xu, H.; Muto, K.; Yamaguchi, J.; Zhao, C.; Itami, K.; Musaev, D. G. *J. Am. Chem. Soc.* **2014**, *136*, 14834–14844. (x) Bair, J. S.; Schramm, Y.; Sergeev, A. G.; Clot, E.; Eisenstein, O.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 13098–13101.

(4) For selected examples of nickel-catalyzed directed C–H bond activation, see: (a) Nakao, Y.; Morita, E.; Idei, H.; Hiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 3264–3267. (b) Ogata, K.; Atsumi, Y.; Shimada, D.; Fukuzawa, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 5896–5899. (c) Shacklady-McAtee, D. M.; Dasgupta, S.; Watson, M. P. *Org. Lett.* **2011**, *13*, 3490–3493. (d) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952–14955. (e) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308–5311. (f) Song, W.; Ackermann, L. *Chem. Commun.* **2013**, 49, 6638–6640. (g) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898–901. (h) Aihara, Y.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 15509–15512. (i) Cong, X.; Li, Y.; Wei, Y.; Zeng, X. *Org. Lett.* **2014**, *16*, 3926–3929. (j) Li, M.; Dong, J.; Huang, X.; Li, K.; Wu, Q.; Song, F.; You, J. *Chem. Commun.* **2014**, 50, 3944–3946. (k) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2014**, *136*, 1789–1792. (l) Yokota, A.; Aihara, Y.; Chatani, N. *J. Org. Chem.* **2014**, *79*, 11922–11932. (m) Iyanaga, M.; Aihara, Y.; Chatani, N. *J. Org. Chem.* **2014**, *79*, 11933–11939. (n) Li, M.; Yang, Y.; Zhou, D.; Wan, D.; You, J. *Org. Lett.* **2015**, *17*, 2546–2549. (o) Lin, C.; Li, D.; Wang, B.; Yao, J.; Zhang, Y. *Org. Lett.* **2015**, *17*, 1328–1331. (p) Lin, C.; Yu, W.; Yao, J.; Wang, B.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 1340–1343. (q) Wang, X.; Qiu, R.; Yan, C.; Reddy, V. P.; Zhu, L.; Xu, X.; Yin, S.-F. *Org. Lett.* **2015**, *17*, 1970–1973. (r) Xiao, J.; Chen, T.; Han, L.-B. *Org. Lett.* **2015**, *17*, 812–815. (s) Yan, Q.; Chen, Z.; Yu, W.; Yin, H.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 2482–2485. (t) Uemura, T.; Yamaguchi, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 3162–3165. (u) Misal Castro, L. C.; Obata, A.; Aihara, Y.; Chatani, N. *Chem. - Eur. J.* **2016**, *22*, 1362–1367. (v) Kubo, T.; Chatani, N. *Org. Lett.* **2016**, *18*, 1698–1701. (w) Aihara, Y.; Chatani, N. *ACS Catal.* **2016**,

- 6, 4323–4329. (x) Ruan, Z.; Lackner, S.; Ackermann, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 3153–3157. (y) Ruan, Z.; Lackner, S.; Ackermann, L. *ACS Catal.* **2016**, *6*, 4690–4693.
- (5) (a) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726–11743. (b) Corbet, M.; De Campo, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 9896–9898.
- (6) For selected recent reviews on functionalization of C–H bonds, see: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345. (c) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651–3678. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (e) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740–4761.
- (7) For selected reviews on PAHs, see: (a) Mitschke, U.; Bäuerle, P. *J. Mater. Chem.* **2000**, *10*, 1471–1507. (b) Watson, M. D.; Fechtenkötter, A.; Müllen, K. *Chem. Rev.* **2001**, *101*, 1267–1300. (c) Bendikov, M.; Wudl, F.; Perepichka, D. F. *Chem. Rev.* **2004**, *104*, 4891–4945. (d) Anthony, J. E. *Chem. Rev.* **2006**, *106*, 5028–5048. (e) Cicoira, F.; Santato, C. *Adv. Funct. Mater.* **2007**, *17*, 3421–3434. (f) Allard, S.; Forster, M.; Souharce, B.; Thiem, H.; Scherf, U. *Angew. Chem., Int. Ed.* **2008**, *47*, 4070–4098. (g) Anthony, J. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 452–483. (h) Wang, C.; Dong, H.; Hu, W.; Liu, Y.; Zhu, D. *Chem. Rev.* **2012**, *112*, 2208–2267. (i) Watanabe, M.; Chen, K.-Y.; Chang, Y. J.; Chow, T. J. *Acc. Chem. Res.* **2013**, *46*, 1606–1615.
- (8) For selected examples of PAHs synthesis, see: (a) Yasukawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 12680–12681. (b) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 2337–2340. (c) Yamashita, M.; Horiguchi, H.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7481–7488. (d) Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 2867–2874. (e) Shi, Z.; Tang, C.; Jiao, N. *Adv. Synth. Catal.* **2012**, *354*, 2695–2700. (f) Tan, X.; Liu, B.; Li, X.; Li, B.; Xu, S.; Song, H.; Wang, B. *J. Am. Chem. Soc.* **2012**, *134*, 16163–16166. (g) Jafarpour, F.; Hazrati, H.; Nouraldinmoussa, S. *Org. Lett.* **2013**, *15*, 3816–3819. (h) Zheng, J.; You, S.-L. *Chem. Commun.* **2014**, *50*, 8204–8207. (i) Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 6557–6559.
- (9) For recent reviews on synthesis of extended  $\pi$ -systems through C–H activation, see: (a) Segawa, Y.; Maekawa, T.; Itami, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 66–81. For selected examples: (b) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 14622–14623. (c) Mitamura, Y.; Yorimitsu, H.; Oshima, K.; Osuka, A. *Chem. Sci.* **2011**, *2*, 2017–2021. (d) Mochida, K.; Kawasumi, K.; Segawa, Y.; Itami, K. *J. Am. Chem. Soc.* **2011**, *133*, 10716–10719. (e) Zhang, Q.; Kawasumi, K.; Segawa, Y.; Itami, K.; Scott, L. T. *J. Am. Chem. Soc.* **2012**, *134*, 15664–15667. (f) Kawasumi, K.; Zhang, Q.; Segawa, Y.; Scott, L. T.; Itami, K. *Nat. Chem.* **2013**, *5*, 739–744. (g) Maekawa, T.; Segawa, Y.; Itami, K. *Chem. Sci.* **2013**, *4*, 2369–2373. (h) Zhao, J.; Oniwa, K.; Asao, N.; Yamamoto, Y.; Jin, T. *J. Am. Chem. Soc.* **2013**, *135*, 10222–10225. (i) Zhao, J.; Asao, N.; Yamamoto, Y.; Jin, T. *J. Am. Chem. Soc.* **2014**, *136*, 9540–9543. (j) Fujikawa, T.; Segawa, Y.; Itami, K. *J. Am. Chem. Soc.* **2015**, *137*, 7763–7768. (k) Morioka, R.; Nobushige, K.; Satoh, T.; Hirano, K.; Miura, M. *Org. Lett.* **2015**, *17*, 3130–3133.
- (10) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019–4022.
- (11) Wu, Y.-T.; Huang, K.-H.; Shin, C.-C.; Wu, T.-C. *Chem. - Eur. J.* **2008**, *14*, 6697–6703.
- (12) Pham, M. V.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 3484–3487.
- (13) Ilies, L.; Matsumoto, A.; Kobayashi, M.; Yoshikai, N.; Nakamura, E. *Synlett* **2012**, *23*, 2381–2384.
- (14) (a) Kajita, Y.; Matsubara, S.; Kurahashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 6058–6059. (b) Kurahashi, T.; Matsubara, S. *Acc. Chem. Res.* **2015**, *48*, 1703–1716.
- (15) (a) Miura, T.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085–3088. (b) Miura, T.; Yamauchi, M.; Murakami, M. *Chem. Commun.* **2009**, 1470–1471. (c) Yamauchi, M.; Morimoto, M.; Miura, T.; Murakami, M. *J. Am. Chem. Soc.* **2010**, *132*, 54–55. (d) Miura, T.; Yamauchi, M.; Kosaka, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4955–4957. (e) Miura, T.; Morimoto, M.; Yamauchi, M.; Murakami, M. *J. Org. Chem.* **2010**, *75*, 5359–5362.
- (16) (a) Korivi, R. P.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 5179–5182. (b) Liu, C.-C.; Parthasarathy, K.; Cheng, C.-H. *Org. Lett.* **2010**, *12*, 3518–3521.
- (17) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840–871.
- (18) For the property and application of fluoranthenes, see: (a) Xia, Z.-Y.; Su, J.-H.; Fan, H.-H.; Cheah, K.-W.; Tian, H.; Chen, C. H. *J. Phys. Chem. C* **2010**, *114*, 11602–11606. (b) Steinberg, B. D.; Jackson, E. A.; Filatov, A. S.; Wakamiya, A.; Petrukina, M. A.; Scott, L. T. *J. Am. Chem. Soc.* **2009**, *131*, 10537–10545. (c) Debad, J. D.; Morris, J. C.; Lynch, V.; Magnus, P.; Bard, A. J. *J. Am. Chem. Soc.* **1996**, *118*, 2374–2379. (d) Saranya, G.; Kolandaivel, P.; Senthilkumar, K. *J. Phys. Chem. A* **2011**, *115*, 14647–14656. (e) Wu, T.-C.; Hsin, H.-J.; Kuo, M.-Y.; Li, C.-H.; Wu, Y.-T. *J. Am. Chem. Soc.* **2011**, *133*, 16319–16321. (f) Wu, T.-C.; Chen, M.-K.; Lee, Y.-W.; Kuo, M.-Y.; Wu, Y.-T. *Angew. Chem., Int. Ed.* **2013**, *52*, 1289–1293.
- (19) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066–3072.
- (20) For a tutorial review on linear free-energy relationship (LFER), see: (a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195. For selected examples: (b) Sigman, M. S.; Miller, J. J. *J. Org. Chem.* **2009**, *74*, 7633–7643. (c) Jensen, K. H.; Sigman, M. S. *J. Org. Chem.* **2010**, *75*, 7194–7201. (d) Michel, B. W.; Steffens, L. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 8317–8325. (e) Harper, K. C.; Sigman, M. S. *J. Org. Chem.* **2013**, *78*, 2813–2818.