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Chromium(III)-catalyzed C(sp^2)–H Alkynylation, Allylation, and Naphthalenation of Secondary Amides with Trimethylaluminum as Base

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Supporting Information Placeholder

ABSTRACT: Among base metals used for C–H activation reactions, chromium(III) is rather unexplored despite its natural abundance and low toxicity. We report herein chromium(III)-catalyzed C(sp^2)–H functionalization of an *ortho*-position of aromatic and α,β-unsaturated secondary amides using readily available $AlMe_3$ as a base, and using bromoalkynes, allyl bromide, and 1,4-dihydro-1,4-epoxynaphthalene as electrophiles. This redox-neutral reaction taking place at 70–90 °C requires as low as 1–2 mol% of $CrCl_3$ or $Cr(acac)_3$ as a catalyst without any added ligand, and tolerates functional groups such as aryl iodide, boronate, and thiophene groups. Stoichiometric and kinetics studies as well as kinetic isotope effects suggest that the catalytic cycle consists of a series of thermally stable but reactive intermediates bearing two molecules of the amide substrate on one chromium atom, and also that one of these chromate(III) complexs takes part in the alkynylation, allylation, and naphthalenation reactions. The proposed mechanism accounts for the effective suppression of methyl group delivery from $AlMe_3$ for *ortho*-C–H methylation.

INTRODUCTION

Base-metal-catalyzed deprotonative C–H activation[1] is a rapidly growing part of the modern C–H activation toolkit,[2] where an organometallic base deprotonates the C–H bond of the substrate to generate a cyclometallated intermediate[3] made of a high-valent metal center (**A**, Figure 1a). This intermediate may then undergo C–C bond formation either by intermolecular delivery of an R$^-$ group to the metal center following reductive elimination,[4] or by reaction with an external electrophile without changing the oxidation state of the metal.[5] The latter manifold is more synthetically attractive than the former because of the availability of a broad structural variety of shelf-stable electrophiles, as opposed to a limited variety of potentially unstable organometallics for delivery of the R$^-$ group. However, the electrophilic trapping of **A** is often plagued by competitive R$^-$ delivery from a coexisting organometallic base, R–M,[1a] and to suppress this side reaction, the reaction often requires an elaborate design of ligand[6] and organometallic base.[7] In the present study, we propose a combination of a carboxamide, a chromium(III) catalyst, and mildly nucleophilic trimethylaluminum ($AlMe_3$) to solve these problems. Chromium(III) is a stable valence form of this naturally abundant and low toxicity metal, whereas chromium(VI) is highly toxic.[8] Readily available and mildly reactive $AlMe_3$ is the base of choice, and undesired C–H methylation[9] is suppressed. The unique benefits of this mild base have been previously reported in the context of base-metal-catalyzed C–H methylations.[10]

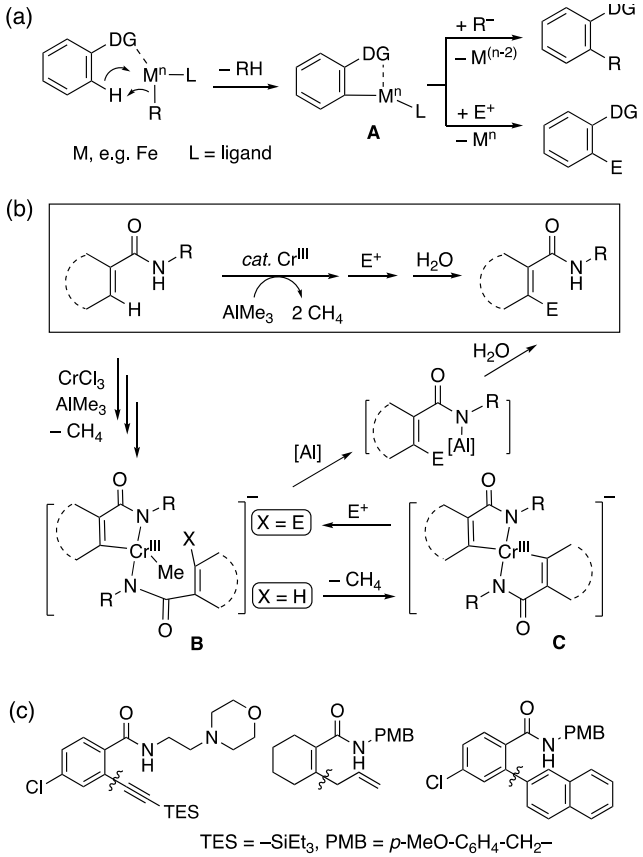


Figure 1. Deprotonative C–H functionalization reactions. (a) Deprotonative C–H activation followed by reductive elimination or electrophile trapping. (b) Chromium(III)-catalyzed C–H functionalization via a reactive biscyclometallated Cr(III) ate complex . The indicated amide coordination to Cr(III) on nitrogen in **B** and **C** is tentative and requires further studies. (c) Representative C–H functionalization products in this study.

We report herein C–H functionalization of aromatic and α,β-unsaturated secondary amides with alkynyl-, allyl-, and aryl electrophiles catalyzed by Cr(III) salts in the presence of a

stoichiometric amount of $AlMe_3$ (Figure 1b), which provides access to a variety of compounds including alkynylated moclobemide, an antidepressant drug (Figure 1c). The reaction is compatible with a variety of functional groups, including ether, amine, ester, boronate, and halide, most notably, aryl iodide functionalitie–a feature reflecting the advantages of this redox-neutral chromium(III)-dominated reaction. The reaction takes place with as little as 1 mol% of an inorganic chromium(III) salt without using extraneous ligand. Stochiometric and kinetics studies as well as kinetic isotope effects suggest that the catalytic cycle consists of a series of thermally stable but reactive intermediates bearing two molecules of the amide substrate on one metal atom such as **B** (X = H or E), and also that one of these chromate(III) complexes (**C**), a biscyclometallated intermediate,[11] takes part in the alkynylation, allylation, and naphthalenation reactions with corresponding electrophiles. The proposed mechanism accounts for effective suppression of methyl group delivery from $AlMe_3$ for *ortho*-C–H methylation. In light of the undervalued utility of chromium among base metals in catalysis,[12] the present result suggests a new direction of research for its use in organic synthesis.[13]

RESULTS AND DISCUSSION

We first describe the alkynylation reaction and the key parameters of this reaction, the allylation, and the naphthalenation, followed by a mechanistic analysis that sheds light on the formation of the biscyclometallated[11, 14] chromium(III) ate complex **C**, and its role in the catalytic cycle.

Alkynylation. The catalytic use of $CrCl_3$ is first described for C–H alkynylation[15] using substituted ethynyl bromide as an electrophile. In Figure 2, we illustrate a gram-scale reaction of *N*-4-methoxybenzyl-3-methylbenzamide (**1**, PMB = 4-methoxybenzyl) using 1.0 mol% of $CrCl_3$ as catalyst and 2.0 equiv of $AlMe_3$ to deliver the desired C–H alkynylation product **3** in 88% isolated yield (1.38 g, 94% yield determined using ^{1}H-NMR). A full conversion of **1** was observed. We found neither a methylated product[10] **4**, nor a dimer[16] **5** in the crude reaction mixture.

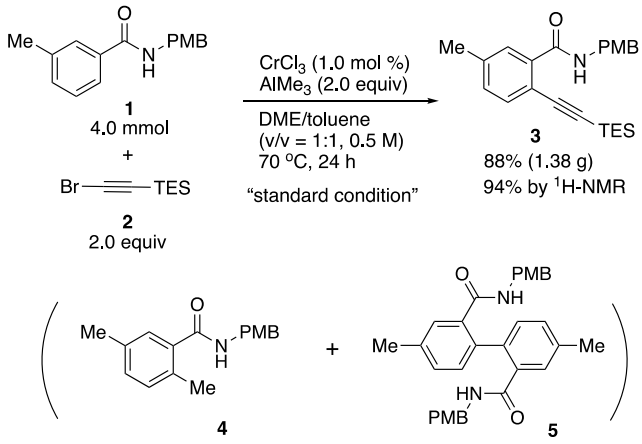


Figure 2. Cr(III)-catalyzed *ortho*-C–H alkynylation of benzamide.

Table 1 shows the key reaction parameters of the Cr(III)-catalyzed C–H alkynylation of the PMB carboxamide **1** with a silylethynyl bromide (see Tables S3 and S4 for other details). Heating a mixture of **1** (1.0 equiv), **2** (2.0 equiv), $CrCl_3$ (10 mol%), and $AlMe_3$ (2.0 equiv) in a mixed toluene and 1,2-DME solvent at 70 ºC under argon resulted in the formation of **3** in 83% isolated yield (89% GC yield) (Table 1, entry 1). The product was free of **4** and **5**. To secure full conversion of the amide substrate, we used two equivalents each of $AlMe_3$ and **2**. The reason for using excess amount of $AlMe_3$ and **2** might be ascribed to the undesired side reaction between them. By contrast, the allylation reaction discussed in Table 3 requires only one equivalent of $AlMe_3$, indicating that two of the three methyl groups potentially act as a base to deprotonate C–H and N–H.

The use of THF as a cosolvent resulted in lower yield and in the formation of the dimer **5** in 16% yield (Table 1, entry 2), while THF was found to be the solvent of choice in the allylation reaction discussed below. The ethereal solvent was found to be essential for the reaction because the reaction did not proceed in toluene alone (entry 3). $Cr(acac)_3$ (70%) and $CrBr_3$ (82%) also served as catalysts (entries 4 and 5). For reasons unknown, however, $Cr(acac)_3$ gave approximately 10% higher yield than $CrCl_3$ for the allylation reactions discussed in the following paragraph. The reaction needs heat and prolonged reaction time, because reducing the temperature or reaction time caused lower conversion (entry 6 and see Supporting Information Table S3 for details). Interestingly, MeMgBr and $ZnMe_2$ failed to give the desired alkynylation product, probably because of the competitive reduction of Cr(III) (entries 7 and 8). $AlEt_3$ and $AlMe_2Cl$ also served as an effective base, but resulted in a reduced yield of **3** (entries 9 and 10). $AlMe_2Cl$ as effective base suggested that the sceond methyl from $AlMe_3$ also participates in the deprotonative C–H activation. Reducing the amount of $AlMe_3$ from 2.0 equiv to 1.5 equiv or 1.0 equiv resulted in a decreased yield of **3**. Additionally, it is worthwhile to mention $FeCl_3$ and $CoCl_2$ were totally ineffective in replacement of $CrCl_3$ under the optimized condition.

Table 1. Chromium(III)-catalyzed Synthesis of 3 by Alkynylation of 1 with 2 under Diverse Catalytic Conditions

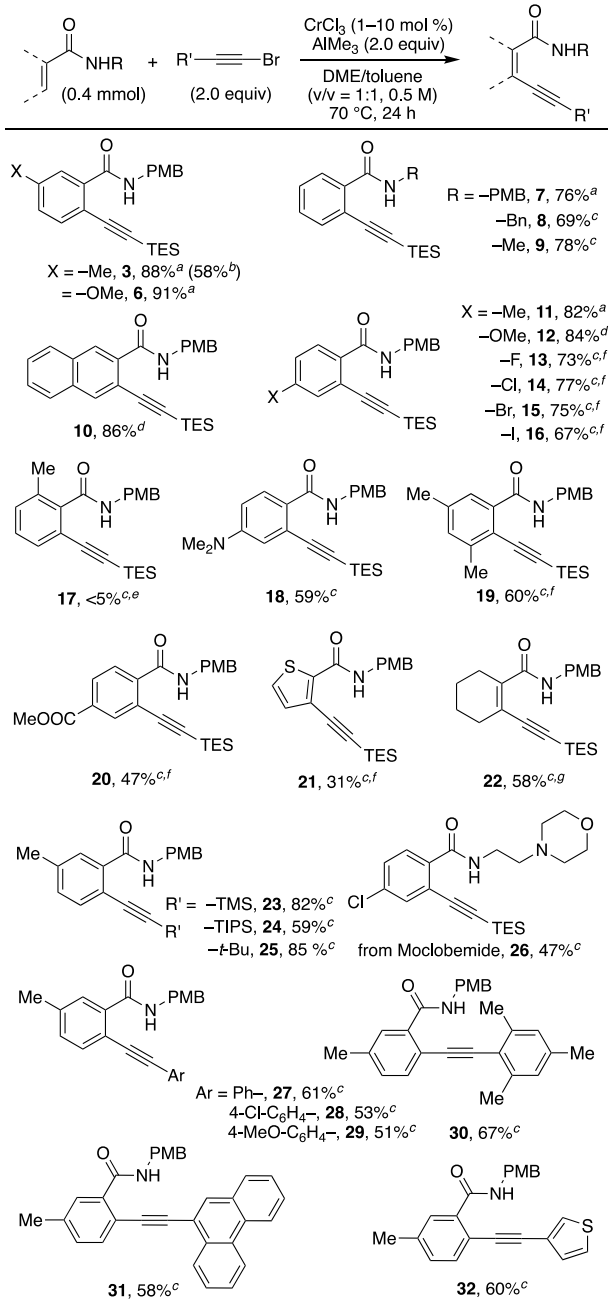
entry	reaction conditions	yield (%)[a]
1	"standard"	89 (83[b])
2[c]	THF instead of DME	78
3	without DME	n.d.
4	$Cr(acac)_3$ instead of $CrCl_3$	70
5	$CrBr_3$ instead of $CrCl_3$	82
6	50 °C instead of 70 °C	54
7[d]	MeMgBr instead of $AlMe_3$	< 5
8	$ZnMe_2$ instead of $AlMe_3$	n.d.
9	$AlEt_3$ instead of $AlMe_3$	63
10[e]	$AlMe_2Cl$ instead of $AlMe_3$	70
11	$AlMe_3$ 1.0 equiv	44
12	$AlMe_3$ 1.5 equiv	68

[a]Standard condition is shown in Figure 2. The yield was determined using GC with tridecane as an internal standard. [b]Yield of isolated product. [c]Dimer **5** formed in 16% yield. [d]THF as a solvent. [e]$AlMe_2Cl$ (3 equiv).

The scope of the C–H alkynylation reaction is illustrated in Table 2. Besides *N*-PMB arene carboxamide (**6, 7**), *N*-benzyl (**8**) and *N*-methyl (**9**) carboxamides also took part in the reaction. The reaction showed exclusive monoselectivity on benzamide and *para*-substituted benzamides, probably because the rigid alkyne substituent on the *ortho*-position prohibits the formation of a chromacycle on the other side (**7**, **11**). Steric hindrance at the *ortho*-position was not tolerated as shown for *o*-toluamide (**17**). Steric hindrance on a *meta*-position (next to the *ortho*-position to be functionalized) is partially tolerated, as shown with 3,5-

dimethylbenzamide producing a C–H alkynylation product in 60% yield (**19**). Such a sterically hindered C–H bond flanked by a methyl group and a directing group was not smoothly cleaved either under iron catalysis applying the bisphosphine ligand we previously reported,[4,5] or under many conditions using a precious-metal catalyst.[17] We ascribe this difference to the small size of the chromium ion and the absence of a bulky ligand on the metal atom.

Table 2. Scope of Chromium(III)-catalyzed C–H Alkynylation



[a]All reactions were performed on a 0.4 mmol scale, and yields refer to the isolated product. $CrCl_3$ (1 mol%). [b]Alkynyl chloride was used instead of alkynyl bromide. [c]$CrCl_3$ (10 mol%). [d]$CrCl_3$ (2 mol%). [e]Yield determined using GC with tridecane as an internal standard. [f]Reactions performed at 90 ºC. [g]THF was used instead of DME at 80 ºC.

The reaction takes place effectively for both electron-rich (**12**, **18**) and electron-deficient (**13**, **20**) substrates, and is compatible with a variety of functional groups, including ether (**12**), aryl halides (**13**–**16**), amine (**18**), and ester (**20**). Interestingly, an aryl iodide moiety is tolerated (**16**) without generating hydrodeiodonation byproduct – a side reaction that sometimes plagues precious-metal catalysis. This iodide tolerance is in agreement with the absence of a reduced chromium species in the catalytic mechanism that we propose in this study.[12f] Thiophene-2-carboxamide gave the desired product in moderate yield (**21**). The reaction also applies to the alkynylation of alkene carboxamide to generate an enyne structure (**22**). Comparison among trimethylsilyl- (**23**), triethylsilyl-substituted (**3**), and triisopropylsilyl (TIPS, **24**) groups suggests a small steric effect. *tert*-Butyl-substituted alkynyl bromides can be used (**23**), while primary and secondary alkyl-substituted alkyne bromides (e.g., *n*-hexyl- and cyclohexyl-) cannot, probably because of the presence of the propargylic C–H bond. The reaction can be used for C–H alkynylation of moclobemide (**26**), a drug for managing depression. Aryl- and heteroaryl-substituted alkynyl bromides gave the desired *ortho*-alkynylation products in moderate yields (**27**–**32**). 2-(Bromoethynyl)-mesitylene gave the highest yield compared with other aryl and heteroaryl-substituted alkynyl bromides, probably because of the enhanced thermal stability of this bromoalkyne by steric hindrance.

N-8-Quinolinyl and *N*-2-picolyl groups that often serve as a directing group for C–H activation inhibited the reaction, probably because the basic nitrogen atoms on the bidentate directing group interfere with the formation of the cyclometallated intermediates. Tertiary benzamides and 2-phenylpyridine, both of which lack an acidic NH group, failed to participate in the reaction.

Allylation. The allylation showed a reaction profile slightly different from that of the alkynylation such as a preference for $Cr(acac)_3$ as catalyst (more soluble), and THF as solvent. Testing a series of allylic electrophiles for *ortho*-C–H allylation[5a,7b,18] showed allylic bromide to be the best allylic electrophile (Figure 3). Allylic chloride and allylic iodide gave lower yields than allylic bromide. Allyl phenyl ether, an electrophile effective for iron-catalyzed *ortho*-C–H allylation,[5a,7b] did not produce the desired C–H allylation product. Allylic acetate did not participate in the reaction, and an allyl phosphate did so in low yield.

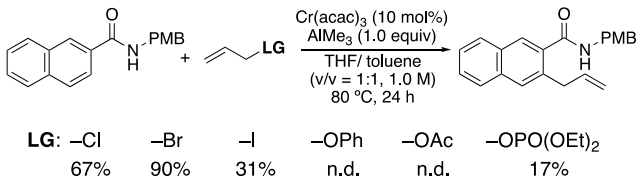
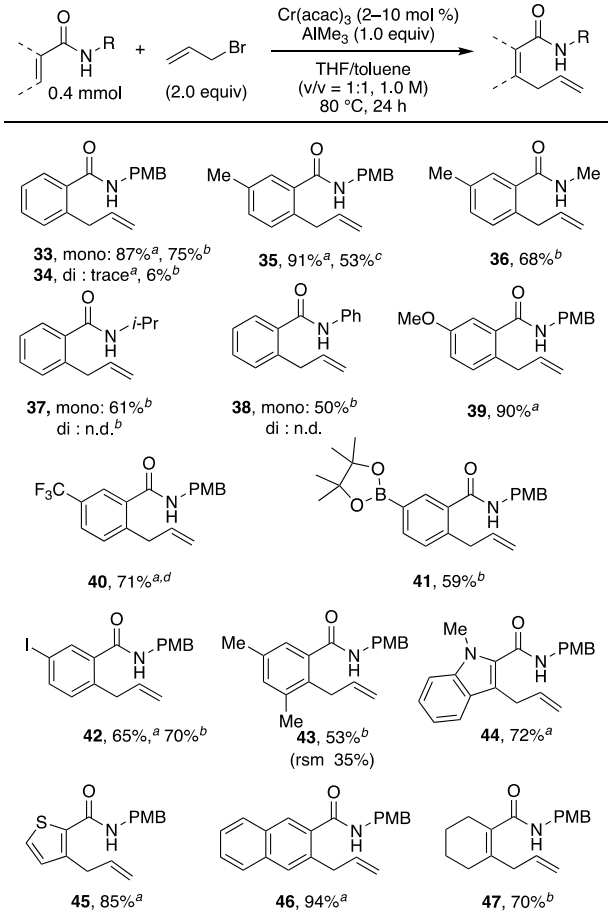


Figure 3. Chromium(III)-catalyzed C–H allylation with different allylic electrophiles

Unlike the C–H alkynylation, the allylation summarized in Table 3 requires only one equivalent of $AlMe_3$ to achieve good to high yield. A small amount of diallylated product was observed for the parent benzamide (**33**, **34**). *N*-Isopropyl and *N*-aryl substituents (**37**, **38**) suppress the diallylation. C–H allylation proceeded well with both electron-rich and electron-deficient amides (**39**, **40**). Aryl pinacol boronate (**41**) and aryl iodide (**42**), substituents useful for further transformation, survived the reaction conditions. Alkenyl carboxamide was allylated to deliver a 1,4-diene product (**47**). In all cases examined, isomerization of C–H allylation products to form styrenyl-type products was not observed under the Cr(III)-catalyzed reaction condition.[19] Substituted allylic bromides such as 2-methylallyl bromide, 3-methyl-2-butenyl bromide, and cinnamyl bromide barely participated in the reaction, suggesting that interaction of the olefinic part of the electrophile with a metal center is crucial for the reaction.

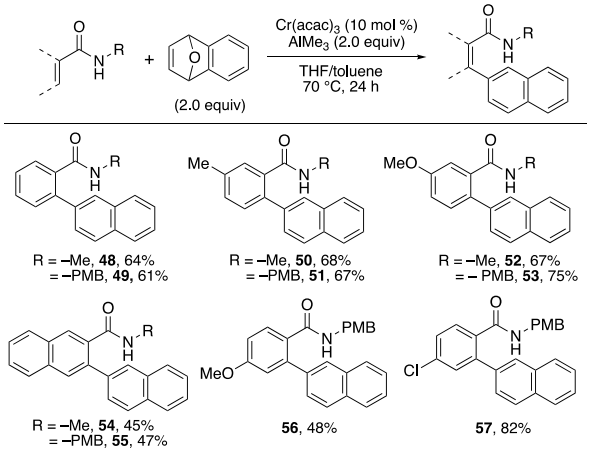
Table 3. Scope of Chromium(III)-catalyzed C–H Allylation with Allylic Bromide



[a]All reactions were performed on a 0.4 mmol scale, and yields refer to the isolated product. $Cr(acac)_3$ used in 2.0 mol %. [b]$Cr(acac)_3$ used in 10 mol % where lower catalyst loading afforded lower yield. [c]$Cr(acac)_3$ used in 1.0 mol %. [d]C–H methylation product was detected in 24% yield.

Naphthalenation. We found that 1,4-dihydro-1,4-epoxynaphthalene serves as a good electrophile to furnish *ortho*-C–H naphthalenation product as shown in Table 4. [20] Both *N*-methylbenzamide and *N*-PMB-substituted benzamide reacted smoothly and gave products in comparable yield (**48** and **49**), and both electron-rich and electron-deficient benzamide were effective substrates (**56** and **57**).

Table 4. Chromium(III)-catalyzed C–H Naphthalenation with 1,4-Dihydro-1,4-epoxynaphthalene



Stochiometric Study of Reactive Cr(III) Intermediates: The present reaction has several unique features among methods for functionalization of unreactive C–H bonds. The reaction does not require any extraneous ligand, taking place with only 1 mol% of $CrCl_3$, and the scope of the electrophile is rather unusual in that only bromoalkynes, allyl bromides, and 1,4-dihydro-1,4-epoxynaphthalene serve as effective electrophiles, whereas common electrophiles such as alkyl halides, and simple and electron-deficient olefins do not. We considered that the nature of the reactive nucleophilic intermediate is worth being probed.

Correlation between the amount of $CrCl_3$ and that of C–H cleavage product (Figure 4) indicated that all of $CrCl_3$ is converted to a stable intermediate of 1:2 Cr/substrate stoichiometry (cf. **C**) in the presence of excess amide substrate. A similar biscyclometallated chromium(III) species has been reported previously.[14] Heating of the amide **1** and *x* mol% of $CrCl_3$ in the presence of one equivalent of $AlMe_3$ at 90 °C for 24 h followed by DCl/D_2O quenching produced partially *ortho*-C–H deuterated **1** in >95% recovery with deuteration ratio approximately equal to *2x* when *x* = 5, 10, 20, and 30. In these experiments (*x* = 5, 10, 20, and 30), neither a methylated product **4** nor an oxidative dimerization product **5** was formed. The use of 50 mol % of $CrCl_3$ resulted in 81% deuterium incorporation and produced **4** and **5** in 2% and 8% yield (mol %), respectively, and the use of 100 mol % $CrCl_3$ resulted in as much as 6% and 21% of **4** and **5**, along with 92% deuterium incorporation in recovered **1**. The results of experiments (*x* = 50, 100) suggested instability of the 1:2 chromacycle **C** in the presence of an excess amount of $CrCl_3$ to either undergo reductive elimination or equilibrate to the 1:1 complex. Note that using $CrCl_2$ did not give any deuterium incorporation and resulted in a full recovery of **1**.

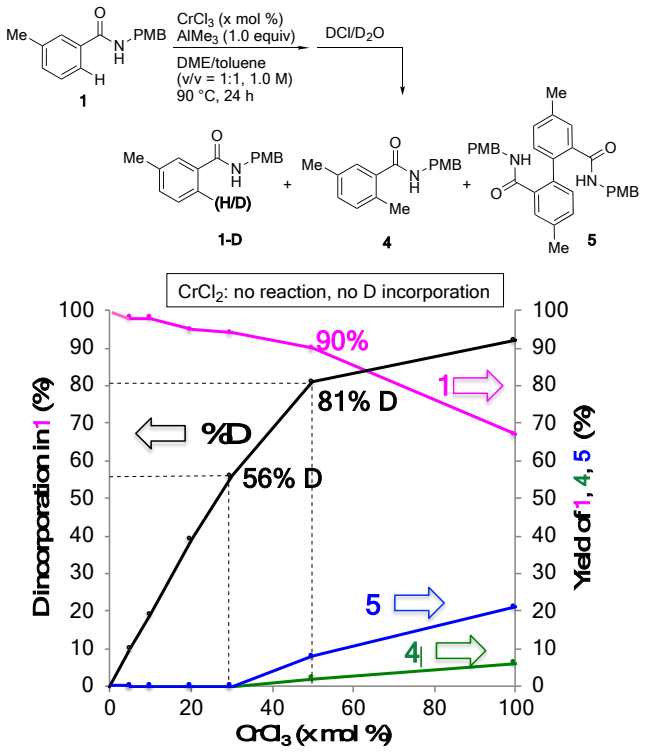


Figure 4. C–H activation/deuteration of **1** with *x* mol% of $CrCl_3$ in the presence of $AlMe_3$

As shown in Figure 5a, the intermediate with a 1:2 Cr/substrate stoichiometry is reactive with bromoacetylene **2** under the same thermal and solvent conditions as those used for the catalytic reaction. The 1:2 complex formed at $x = 50$ reacted with **2** to give the C–H alkynylated product **3** in 42% yield based on the amount of chromium (Figure 5a). A 1:1 Cr:substrate complex formed at $x = 100$ was unreactive toward electrophiles as shown in Figure 5b, c, while high *ortho*-deuteration ratio revealed cleavage of the C–H bond . We surmise that the 1:1 complex formed after C–H cleavage could be a neutral chromium(III) species. This species would not play any significant role in catalysis, where a large excess of the amide substrate converts it to the 1:2 complex **C**. At this stage, we could obtain neither NMR data nor a single crystal suitable for crystallographic analysis for the 1:2 and 1:1 complexes.

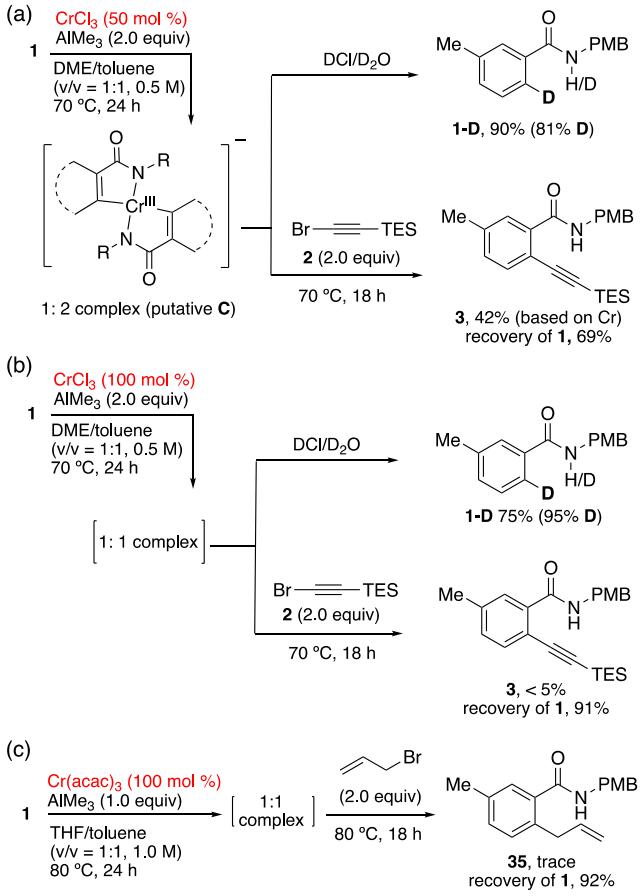


Figure 5. Stochiometric generation of 1:2 and 1:1 Cr(III)/amide complexes.

The 1:2 complex **C** prepared in situ acts as a catalyst for the C–H alkynylation reaction as shown in Figure 6. Deuterium quenching experiments in Figure 4 show generation of a biscyclometallated chromium (III) species upon heating a mixture of $CrCl_3$ (30 mol%), $AlMe_3$ (1.0 equiv), and **1** at 90 ºC for 24 h. It was observed that 10 mol% of **C** generated in situ from 0.40 mmol of **1** effected the C–H coupling between *N*-PMB-*p*-methoxybenzamide (0.40 mmol) and bromoalkyne **2** to give the desired product **12** in 83% yield (0.33 mmol) together with the product **3** derived from **1** in a small amount (0.016 mmol).

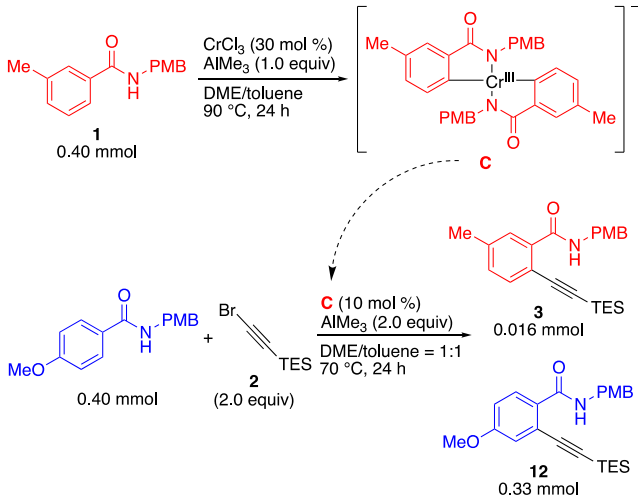
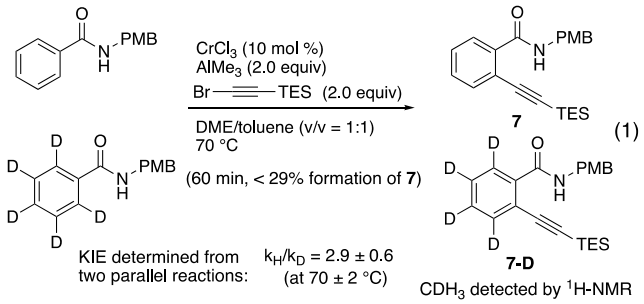
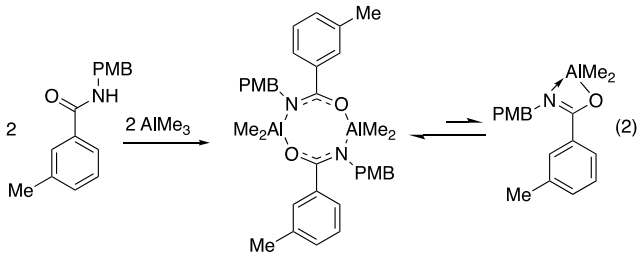


Figure 6. Catalytic activity of biscyclometallated Cr(III) intermediate **C** generated in situ.

Kinetics of the Catalytic Cycle: With the reactivity of intermediates identified in stoichiometric reactions, we next examined the kinetics of the catalytic reaction. Kinetic isotope effect (KIE) experiments on two parallel reactions using a benzamide and its *d5*-derivative showed a primary KIE of 2.9, indicating that cleavage of the C–H bond is the turnover-limiting step of the reaction (Eq. 1). CDH_3 was generated from benzamide-*d5* (detected by ^{1}H-NMR analysis), proving unambiguously that the methyl group on $AlMe_3$ deprotonated an *ortho*-C–H bond in the amide. The reaction was not affected by the addition of a radical scavenger such as 1,1-diphenylethylene and 9,10-dihydroanthracene (see Supporting Information Fig. S6 for details), eliminating the possibility of a free radical mechanism.



The kinetic orders of the alkynylation of amide **1** with the bromoalkyne **2**, as determined for chromium, **1**, $AlMe_3$, and **3** using $Cr(acac)_3$ as a Cr(III) source soluble in DME/toluene (Figure 7), is consistent with the KIE data (Eq. 1) in that the C–H activation is the slowest step in the catalytic cycle. Details of the analysis are shown in Supporting Information. The reaction was found to be first order in $Cr(acac)_3$ (Figure 7a) and half order in the amide **1** (Figure 7b). As shown in Figure 7c, the reaction occurs only at >1:1 stoichiometry between $AlMe_3$ and **1**. These findings agree well with the results of crystallographic studies on the formation of a stable dimeric complex from a secondary amide and $AlMe_3$ (cf. Eq. 2),[21] from which a reactive monomer reversibly forms and takes part in the catalytic cycle. The reaction was found to be 0.38 order in the bromoalkyne **2**, suggesting reversible coordination of the alkyne to a chromium species in the catalytic cycle.



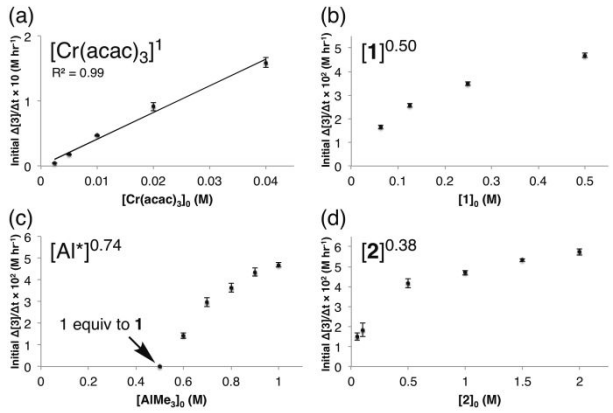


Figure 7. Kinetics of the *ortho*-C–H alkynylation of amide **1** with bromoacetylene **2** in the presence of $AlMe_3$ and $Cr(acac)_3$ in DME/toluene (1:1) at 70 ºC. The initial rate (Δ[**3**]/Δt) was plotted against the initial concentration of the reactant varied for the range shown below. (a) Initial reaction rate against the initial concentration of $Cr(acac)_3$ $[Cr(acac)_3]_0$. Reaction conditions: **1** (0.50 M), **2** (1.0 M), $Cr(acac)_3$ (2.5×10^{-3}–4.0×10^{-2} M), $AlMe_3$ (1.0 M), DME/toluene (1:1), 70 ºC, up to 4 h; (b) Initial reaction rate against the initial concentration of amide $[\mathbf{1}]_0$. Reaction conditions: **1** (0.063–0.50 M), **2** (1.0 M), $Cr(acac)_3$ (0.010 M), $AlMe_3$ (1.0 M), DME/toluene (1:1), 70 ºC, up to 4 h; (c) Initial reaction rate against the initial concentration of $AlMe_3$ $[AlMe_3]_0$. $[Al^*]_0 = [AlMe_3]_0 - 0.5$ M. Reaction conditions: **1** (0.50 M), **2** (1.0 M), $Cr(acac)_3$ (0.010 M), $AlMe_3$ (0.50–1.0 M), DME/toluene (1:1), 70 ºC, up to 4 h; (d) Initial reaction rate against the initial concentration of alkyne $[\mathbf{2}]_0$. Reaction conditions: **1** (0.50 M), **2** (0.050–2.0 M), $Cr(acac)_3$ (0.010 M), $AlMe_3$ (1.0 M), DME/toluene (1:1), 70 ºC, up to 4 h.

Based on the KIE and the kinetics data, we suggest a catalytic cycle in Figure 8a. At the very beginning of the reaction, an aluminum amide dimer reversibly dissociates into a monomer **I** (top left) that quickly reacts with the inorganic chromium salt to form the chromate(III) complex **C** (which may be the same as **III** in the catalytic cycle). Once the cycle starts, **I** undergoes quick ligand exchange with an alkynylated chromate(III) anion (**VI**) to form the product **VII** and the first key Me–Cr(III) intermediate **II** (i.e., **B** (X = H) in Figure 1b). The turn-over limiting C–H activation within **II** may occur via a deprotonation mechanism (**TS1**, Figure 8b), similarly to organoiron(III) ate species,[1a] to produce the second key intermediate, the 1:2 complex **III** (i.e., **C** in Figure 1b) that undergoes alkynylation via a chromate(III)/alkyne complex **IV**. The mechanism of the alkynylation (**TS2**) on chromate species may resemble the transition state of the alkenylation of $R_2Cu(I)Li$ that takes place via a cuprio(III)cyclopropane intermediate (Figure 8c).[22] A chromium(III) bromide **V** generated in this step quickly reacts with $AlMe_3$ to form **VI** (i.e., **B** (X = E) in Figure 1b), which generates

the aluminum amide product **VII** upon transmetallation with **I** to complete the catalytic cycle.

In the catalytic cycle using 1–2 mol% Cr(III), we see a reason for the exclusive formation of the desired product, and the absence of either C–H methylation (**4**) or the dimerization side reactions (**5**); that is, the Cr(III) center always bears four anionic ligands and the system remains in a reductive environment throughout the cycle. We saw **4** and **5** only when we used an unnecessary excess Cr(III) (refer to Figure 4).

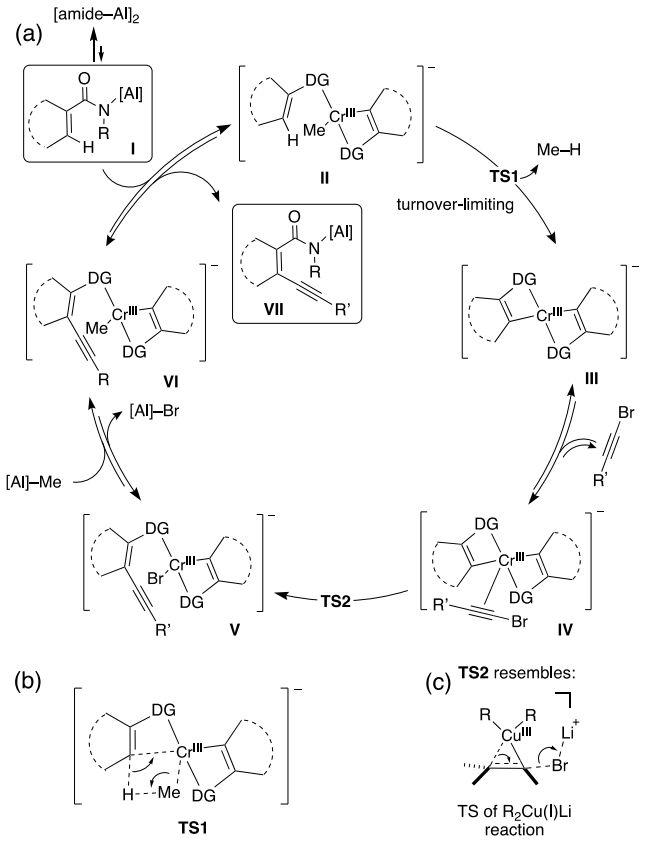


Figure 8. Mechanistic insights. (a) Proposed catalytic cycle. (b) A transition state model for C–H activation. (c) Theory-based transition state model of alkenylation of $R_2Cu(I)^-$ that resembles the proposed transition state of the chromate species reacting with an unsaturated electrophile.

CONCLUSION

In summary, we found that 1–2 mol% of $CrCl_3$ or $Cr(acac)_3$ combined with $AlMe_3$ as a base cleaves *ortho*-C–H bonds of aromatic and α,β-unsaturated secondary carboxamides to achieve direct conversion of a C–H bond into an alkynyl, allyl, and aryl group by reaction with the corresponding electrophile. The substrate itself serves as a ligand for the chromium atom (Figure 8) forming a nucleophilic chromate(III) complex with a 1:2 ratio of Cr/amide under the catalytic conditions; hence, the reaction does not need any additional ligand. The present redox-neutral chromium(III)-catalyzed reaction is compatible with a variety of functional groups, including aryl iodide, aryl boronate, and thiophene ring. Further exploration of the chromium/aluminum reaction system in organic synthesis will bring this undervalued base metal to chemists' attention.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and physical properties of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(a) Shang, R.; Ilies, L.; Nakamura, E. Iron-Catalyzed C–H Bond Activation. *Chem. Rev.* **2017**, *117*, 9086–9139; (b) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C–H Activation. *Chem. Rev.* **2019**, *119*, 2192–2452; (c) Nakamura, E.; Sato, K. Managing the Scarcity of Chemical Elements. *Nat. Mater.* **2011**, *10*, 158–161.

[2] Selected reviews: (a) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Perterson, T. H. Selective Intermolecular Carbon—Hydrogen Bond Activation by Synthetic Metal Complexes in Homogeneous Solution. *Acc. Chem. Res.* **1995**, *28*, 154–162; (b) Shilov, A. E.; Shul'pin, G. B. Activation of C–H Bonds by Metal Complexes. *Chem. Rev.* **1997**, *97*, 2879–2932; (c) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C–H Functionalization Reactions. *Chem. Rev.* **2010**, *110*, 1147–1169; (d) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild Metal-catalyzed C–H Activation: Examples and Concepts. *Chem. Soc. Rev.,* **2016**, *45*, 2900–2936; (e) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. Transition-metal catalyzed alkylation using alkenes. *Chem. Rev.* **2017**, *117*, 9333–9403; (f) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. Palladium-Catalyzed Transformations of Alkyl C–H Bonds. *Chem. Rev.* **2017**, *117*, 8754–8786.

[3] Albrecht, M. Cyclometalation Using *d*-Block Transition Metals: Fundamental Aspects and Recent Trends. *Chem. Rev*., **2010**, *110*, 576–623.

[4] (a) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. Iron-Catalyzed Direct Arylation through Directed C–H Bond Activation. *J. Am. Chem. Soc.* **2008**, *130*, 5858–5859; (b) Shang, R.; Ilies, L.; Nakamura, E. *β*-Arylation of Carboxamides via Iron-Catalyzed C(sp3)–H Bond Activation. *J. Am. Chem. Soc.* **2013**, *135*, 6030–6032; (c) Shang, R.; Ilies, L.; Asako, S.; Nakamura, E. Iron-Catalyzed $C(sp^2)$–H Bond Functionalization with Organoboron Compounds. *J. Am. Chem. Soc.* **2014**, *136***,** 14349–14352; (d) Fruchey, E. R.; Monks, B. M.; Cook, S. P. A Unified Strategy for Iron-Catalyzed *orthro*-Alkylation of Carboxamides. *J. Am. Chem. Soc.* **2014**, *136,* 13130–13133; (e) Doba, T.; Matsubara, T.; Ilies, L.; Shang, R.; Nakamura, E. Homocoupling-free Iron-catalysed Twofold C–H Activation/cross-couplings of Aromatics via Transient Connection of Reactants. *Nat. Catal*. **2019**, *2*, 400–406.

[5] (a) Asako, S.; Norinder, J.; Ilies, L.; Yoshikai, N.; Nakamura, E. *ortho*-Allylation of 1-Arylpyrazoles with Allyl Phenyl Ether *via* Iron-Catalyzed C–H Bond Activation under Mild Conditions. *Adv. Synth. Catal.* **2014**, *356*,

1481–1485; (b) Monks, B. M.; Fruchey, E. R.; Cook, S. P. Iron-Catalyzed C(sp^2)–H Alkylation of Carboxamides with Primary Electrophiles. *Angew. Chem., Int. Ed.* **2014**, *53*, 11065–11069; (c) Ilies, L.; Zhou, Y.; Yang, H. T.; Matsubara, T.; Shang, R.; Nakamura, E. Iron-Catalyzed Directed Alkylation of Carboxamides with Olefins via a Carbometalation Pathway. *ACS Catal.* **2018**, *8*, 11478–11482.

[6] (a) Gao, K.; Lee, P.-S.; Long, C.; Yoshikai, N. Cobalt-Catalyzed *Ortho*-Arylation of Aromatic Imines with Aryl Chlorides. *Org. Lett.* **2012**, *14*, 4234–4237; (b) Song, W.; Ackermann, L. Cobalt-Catalyzed Direct Arylation and Benzylation by C–H/C–O Cleavage with Sulfamates, Carbamates, and Phosphates. *Angew. Chem., Int. Ed.* **2012**, *51*, 8251–8254; (c) Gao, K.; Yoshikai, N. Low-Valent Cobalt Catalysis: New Opportunities for C−H Functionalization. *Acc. Chem. Res.* **2014**, *47*, 1208–1219.

[7] (a) Powell, D. A.; Maki, T.; Fu, G. C. Stille Cross-Couplings of Unactivated Secondary Alkyl Halides Using Monoorganotin Reagents. *J. Am. Chem. Soc*. **2005,** *127*, 510–511; (b) Asako, S.; Ilies, L.; Nakamura, E. Iron-Catalyzed *ortho*-Allylation of Aromatic Carboxamides with Allyl Ethers. *J. Am. Chem. Soc.* **2013**, *135*, 17755–17757.

[8] Barceloux, D. G. Chromium. *J. Toxicol. Clin. Toxicol.* **1999**, *37*, 173–194.

[9] (a) Li, B.; Wu, Z.-H.; Gu, Y.-F.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. Direct Cross-Coupling of C–H Bonds with Grignard Reagents through Cobalt Catalysis. *Angew. Chem. Int. Ed.* **2011**, *50*, 1109–1113. (b) Uemura, T. Yamaguchi, M. Chatani, N. Phenyltrimethylammonium Salts as Methylation Reagents in the Nickel-Catalyzed Methylation of C–H Bonds. *Angew. Chem. Int. Ed.* **2016**, *55*, 3162–3165; (c) Schönherr, H.; Cernak, T. Profound Methyl Effects in Drug Discovery and a Call for New C–H Methylation Reactions. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256–12267.

[10] (a) Shang, R.; Ilies, L.; Nakamura, E. Iron-Catalyzed Directed C(sp^2)–H and C(sp^3)–H Functionalization with Trimethylaluminum. *J. Am. Chem. Soc*. **2015**, *137*, 7660–7663; (b) Ilies, L.; Ichikawa, S.; Asako, S.; Matsubara, T.; Nakamura, E. Iron-Catalyzed Directed Alkylation of Alkenes and Arenes with Alkylzinc Halides. *Adv. Synth. Catal.* **2015**, *357,* 2175–2179; (c) Graczyk, K.; Haven, T.; Ackermann, L. Iron-Catalyzed C(sp^2)–H and C(sp^3)–H Methylations of Amidesand Anilides. *Chem. Eur. J.* **2015**, *21*, 8812–8815; (d) Shang, R.; Ilies, L.; Nakamura, E. Iron-Catalyzed *Ortho* C−H Methylation of Aromatics Bearing a Simple Carbonyl Group with Methylaluminum and Tridentate Phosphine Ligand. *J. Am. Chem, Soc.* **2016**, *138,* 10132–10135; (e) Wang, H.; Zhang, S.; Wang, Z.; He, M.; Xu, K. Cobalt-Catalyzed Monoselective *Ortho*-C–H Functionalization of Carboxamides with Organoaluminum Reagent. *Org. Lett.* **2016**, *18*, 5628–5631.

[11] Simonetti, M.; Cannas, D. M.; Just-Baringo, X.; Vitorica-Yrezabal, I. J.; Larrosa, I. Cyclometallated Ruthenium Catalyst enables Late-stage Directed Arylation of Pharmaceuticals. *Nat. Chem.* **2018**, *10*, 724–731.

[12] (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. Grignard-type Carbonyl Addition of Allyl Halides by means of Chromous Salt. A Chemospecific Synthesis of Homoallyl Alcohols. *J. Am. Chem. Soc*. **1977**, *99*, 3179–3181; (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. Catalytic Effect of Nickel(II) Chloride and Palladium(II) Acetate on Chromium(II)-mediated Coupling Reaction of Iodo Olefins with Aldehydes. *J. Am. Chem. Soc.* **1986**, *108*, 5644–5646; (c) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. Reactions of Alkenylchromium Reagents Prepared from Alkenyl Trifluoromethanesulfonates (triflates) with Chromium(II) Chloride under Nickel Catalysis. *J. Am. Chem. Soc.* **1986**, *108*, 6048–6050; (d) Theopold, K. H. Organochromium(III) Chemistry: A Neglected Oxidation State. *Acc. Chem. Res.* **1990**, *23*, 263–270; (e) Suh, E. M.; Kishi, Y. Synthesis of Palytoxin from Palytoxin Carboxylic Acid. *J. Am. Chem. Soc.* **1994**, *116*, 11205–11206; (f) Fürstner, A.; Shi, N. Nozaki−Hiyama−Kishi Reactions Catalytic in Chromium. *J. Am. Chem. Soc.* **1996**, *118*, 12349–12357; (g) Fürstner A. Carbon-Carbon Bond Formations Involving Organochromium(III) Reagents. *Chem. Rev*. **1999**, *99*, 991–1046; (h) Steib, A. K.; Kuzmina, O. M.; Fernandez, S.; Flubacher, D.; Knochel, P. Efficient Chromium(II)-Catalyzed Cross-Coupling Reactions between Csp^2 Centers. *J. Am. Chem. Soc.* **2013**, *135*, 15346–15349; (i) Cong, X.; Fan, F.; Ma, P.; Luo, M.; Chen, H.; Zeng, X. Low-Valent, High-Spin Chromium-Catalyzed Cleavage of Aromatic Carbon−Nitrogen Bonds at Room Temperature: A Combined Experimental and Theoretical Study. *J. Am. Chem. Soc.* **2017**, *139*, 15182–15190; (j) Han, B.; Ma, P.; Cong, X.; Chen, H.; Zeng, X. Chromium- and Cobalt-Catalyzed, Regiocontrolled Hydrogenation of Polycyclic Aromatic Hydrocarbons: A Combined Experimental and Theoretical Study. *J. Am. Chem. Soc*. **2019**, *141*, 9018–9026.

[13] (a) MacAdams, L. A.; Kim, W.-K.; Liable-Sands, L. M.; Guzei, I. A.; Rheingold, A. L.; Theopold, K. H. The $(Ph)_2$nacnac Ligand in Organochromium Chemistry. *Organometallics* **2002**, *21*, 952–960; (b) Kuzmina, O. M.; Knochel, P. Room-Temperature Chromium(II)-Catalyzed Direct Arylation of Pyridines, Aryl Oxazolines, and Imines Using Arylmagnesium Reagents. *Org. Lett.* **2014**, *16*, 5208−5211; (c) Li, Y.; Deng, G.; Zeng, X. Chromium-Catalyzed Regioselective Hydropyridination of Styrenes. *Organometallics* **2016**, *35*, 747−750; (d) Tanga, J.; Luo, M.; Zeng, X. Chromium-catalyzed, Regioselective Cross-coupling of C–O Bonds by using Organic Bromides as Reactants. *Synlett* **2017**, *28*, 2577–2580; (e) Yan, J.; Yoshikai, N. Chromium-catalyzed Migratory Arylmagnesiation of Unactivated Alkynes. *Org. Chem. Front.* **2017**, *4*, 1972–1975; (f) Yan, J. M.; Yoshikai, N. Phenanthrene Synthesis via Chromium-Catalyzed Annulation of 2-Biaryl Grignard Reagents and Alkynes. *Org. Lett*. **2017**, *19*, 6630–6633; (g) Liu, P.; Chen, C.; Cong, X.; Tang, J.; Zeng, X. Chromium-catalyzed *para*-Selective Formation of Quaternary Carbon Centers by Alkylation of Benzamide Derivatives. *Nat. Commun*., **2018**, *9*, 4637–4644; (h) Tang, J.; Liu, P.; Zeng, X. *N*-Heterocyclic Carbene-chromium-catalyzed Alkylative Cross-coupling of Benzamide Derivatives with Aliphatic Bromides. *Chem. Commun*., **2018**, *54*, 9325–9328; (i) Li, J.; Knochel, P. Chromium-catalyzed Cross-couplings and Related Reactions. *Synthesis* **2019**, *51*, 2100–2106.

[14] Hirscher, N. A.; Sierra, D. P.; Agapie, T. Robust Chromium Precursors for Catalysis: Isolation and Structure of a Single-Component Ethylene Tetramerization Precatalyst. *J. Am. Chem. Soc*. **2019**, *141*, 6022–6029.

[15] (a) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. Direct Palladium-Catalyzed Alkynylation of N-Fused Heterocycles. *J. Am. Chem. Soc.* **2007**, *129*, 7742−7743; (b) Ano, Y.; Tobisu, M.; Chatani, N. Ruthenium-Catalyzed Direct *ortho*-Alkynylation of Arenes with Chelation Assistance. *Synlett* **2012**, *23*, 2763−2767; (c) Shang, M.; Wang H.-L.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. Cu(II)-Mediated Ortho C−H Alkynylation of (Hetero)Arenes with Terminal Alkynes. *J. Am. Chem. Soc.* **2014**, *136*, 11590−11593; (d) Xie, F.; Qi, Z.; Yu, S.; Li, X. Rh(III)- and Ir(III)-Catalyzed C−H Alkynylation of Arenes under Chelation Assistance. *J. Am. Chem. Soc.* **2014**, *136*, 4780−4787; (e) Zhang, Z.-Z.; Liu, B.; Wang, C.-Y.; Shi, B.-F. Cobalt(III)-Catalyzed C2-Selective C−H Alkynylation of Indoles. *Org. Lett.* **2015**, *17*, 4094−4097; (f) Chen, C.; Liu, P.; Tang, J.; Deng, G.; Zeng, X. Iridium-Catalyzed, Weakly Coordination-Assisted *Ortho*-Alkynylation of (Hetero)aromatic Carboxylic Acids without Cyclization. *Org. Lett.* **2017**, *19*, 2474−2477; (g) Ruan, Z.; Sauermann, N.; Manoni, E.; Ackermann, L. Manganese-catalyzed C–H Alkynylation: Expedient Peptide Synthesis and Modification. *Angew. Chem. Int. Ed.* **2017**, *56*, 3172–3176; (h) Cera, G.; Haven, T.; Ackermann, L. Iron-catalyzed C−H Alkynylation through Triazole Assistance: Expedient Access to Bioactive Heterocycles. *Chem. Eur. J.* **2017**, *23*, 3577–3582. (i) Caspers, L. D.; Nachtsheim, B. J. Directing-group-mediated C−H-Alkynylations. *Chem. Asian. J.* **2018**, *13*, 1231–1242.

[16] (a) Grigorjeva, L.; Daugulis, O. Cobalt-Promoted Dimerization of Aminoquinoline Benzamides. *Org. Lett.* **2015**, *17*, 1204−1207; (b) Wang, M.; Hu, Y.; Jiang, Z.; Shen. H. C.; Sun, X. Divergent Copper-mediated Dimerization and Hydroxylation of Benzamides involving C–H Bond Functionalization. *Org. Biomol. Chem.,* **2016**, *14*, 4239–4246.

[17] (a) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. Versatile Pd(II)-Catalyzed C–H Activation/Aryl-Aryl Coupling of Benzoic and Phenyl Acetic Acids. *J. Am. Chem. Soc*. **2008**, *130,* 17676–17677; (b) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, F. Diverse Strategies toward Indenol and Fulvene Derivatives: Rh-Catalyzed C–H Activation of Aryl Ketones Followed by Coupling with Internal Alkynes. *J. Am. Chem. Soc.* **2011**, *133*, 2154–2156; (c) Sivasakthikumaran, R.; Jambu, S.; Jeganmohan, M. Ruthenium(II)-Catalyzed Distal Weak *O*-Coordinating C−H Alkylation of Arylacetamides with Alkenes: Combined Experimental and DFT Studies. *J. Org. Chem*. **2019**, *84*, 3977–3989; (d) For examples that palladium catalysts cleave sterically hindered C-H bonds, see: Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Constructing Multiply Substituted Arenes using Sequential Palladium(II)-catalyzed C–H Olefination. *Angew. Chem. Int. Ed.* **2010**, *49*, 6169–6173.

[18] (a) Ye, B.; Cramer, N. A Tunable Class of Chiral Cp Ligands for Enantioselective Rhodium(III)-Catalyzed C−H Allylations of Benzamides. *J. Am. Chem. Soc.* **2013**, *135*, 636−639; (b) Yu, D.-G.; Gensch, T.; Azambuja, F.; Vaśquez-Ceśpedes, S.; Glorius, F. Co(III)-Catalyzed C–H Activation/Formal S_N-Type Reactions: Selective and Efficient Cyanation, Halogenation, and Allylation. *J. Am. Chem. Soc.* **2014**, *136*, 17722−17725; (c) Korkis, S. E.; Burns, D. J.; Lam, H. W. Rhodium-Catalyzed Oxidative C−H Allylation of Benzamides with 1,3-Dienes by Allyl-to-Allyl 1,4-Rh(III) Migration. *J. Am. Chem. Soc.* **2016**, *138*, 12252−12257; (d) Cera, G.; Haven, T.; Ackermann, L. Expedient Iron-catalyzed C–H

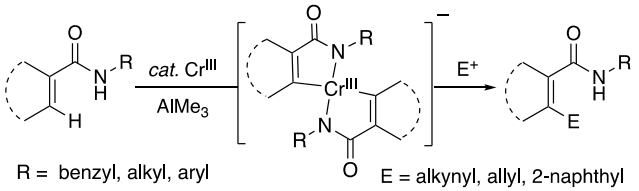
Allylation/alkylation by Triazole Assistance with Ample Scope. *Angew. Chem. Int. Ed.* **2016**, *55*, 1484–1488; (e) Ali, S.; Huo, J.; Wang, C. Manganese-Catalyzed Aromatic C−H Allylation of Ketones. *Org. Lett.* **2019**, *21*, 6961−6965; (f) Achar, T. K.; Zhang, X.; Mondal, R.; Shanavas, M. S.; Maiti, S.; Maity, S.; Pal, N.; Paton, R. S.; Maiti, D. Palladium-catalyzed Directed Meta-selective C–H Allylation of Arenes: Unactivated Internal Olefins as Allyl Surrogates. *Angew. Chem. Int. Ed.* **2019**, *58*, 10353–10360; (g) Baccalini, A.; Vergura, S.; Dolui, P.; Maiti, S.; Dutta, S.; Maity, S.; Khan, F. F.; Lahiri, G. K.; Zanoni, G.; Maiti, D. Cobalt-catalyzed C(sp^2)−H Allylation of Biphenyl Amines with Unbiased Terminal Olefins. *Org. Lett.* **2019**, *21*, 8842−8846.

[19] Hassam, M.; Taher, A.; Arnott, G. E.; Green, I. R.; van Otterlo W. A. L.; Isomerization of Allylbenzenes. *Chem. Rev.* **2015**, *115*, 5462−5569.

[20] (a) Ito, S.; Takahashi, K.; Nozaki, K. Formal Aryne Polymerization: Use of [2.2.1]oxabicyclic Alkenes as Aryne Equivalents. *J. Am. Chem. Soc.* **2014**, *136*, 7547−7550; (b) Cheng, Y.; Parthasarathy, K.; Bolm, C. Rhodium(III)-catalyzed Annulation of *N*-Methoxybenzamides with Heterobicyclic Alkenes by C–H Functionalization: Synthesis of Benzo[*b*]phenanthridinones. *Eur. J. Org. Chem.* **2017**, *2017*, 1203–1206; (c) Qiu, S.; Zhai, S.; Wang, H.; Chen, X.; Zhai, H. One-pot Synthesis of Benzo[*b*]fluorenones via a Cobalt-catalyzed MHP-directed [3+2] Annulation/ring-opening/dehydration Sequence. *Chem. Commun.* **2019**, *55*, 4206–4209.

[21] Huang, B.-H.; Yu, T.-L.; Huang, Y.-L.; Ko, B.-T.; Lin, C.-C. Reactions of Amides with Organoaluminum Compounds: Factors Affecting the Coordination Mode of Aluminum Amidates. *Inorg. Chem.* **2002**, *41*, 2987–2994.

[22] (a) Nakamura, E.; Miyachi, Y.; Koga, N.; Morokuma, K. Theoretical Studies of Heteroatom-Directed Carbometalation. Addition of MeCu, Me_2Cu^-, and MeLi to Substituted Acetylenes. *J. Am. Chem. Soc.* **1992**, *114*, 6686–6692; (b) Yoshikai, N.; Nakamura, E. Mechanism of Substitution Reaction on sp^2-Carbon Center with Lithium Organocuprate. *J. Am. Chem. Soc.* **2004**, *126*, 12264–12265.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R = benzyl, alkyl, aryl
E = alkynyl, allyl, 2-naphthyl