

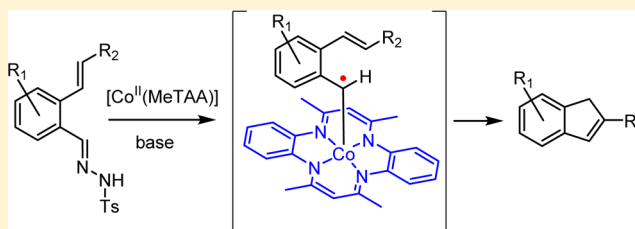
Co^{III}–Carbene Radical Approach to Substituted 1*H*-Indenes

Braja Gopal Das,[†] Andrei Chirila,[†] Moniek Tromp, Joost N. H. Reek, and Bas de Bruin^{*}

Homogeneous, Supramolecular and Bio-Inspired Catalysis (HomKat) Group, Van 't Hoff Institute for Molecular Sciences (HIMS), University of Amsterdam, Science Park 904, 1098 XH Amsterdam, The Netherlands

S Supporting Information

ABSTRACT: A new strategy for the catalytic synthesis of substituted 1*H*-indenes via metalloradical activation of *o*-cinnamyl *N*-tosyl hydrazones is presented, taking advantage of the intrinsic reactivity of a Co^{III} carbene radical intermediate. The reaction uses readily available starting materials and is operationally simple, thus representing a practical method for the construction of functionalized 1*H*-indene derivatives. The cheap and easy to prepare low spin cobalt(II) complex [Co^{II}(MeTAA)] (MeTAA = tetramethyltetraaza[14]annulene) proved to be the most active catalyst among those investigated, which demonstrates catalytic carbene radical reactivity for a nonporphyrin cobalt(II) complex, and for the first time catalytic activity of [Co^{II}(MeTAA)] in general. The methodology has been successfully applied to a broad range of substrates, producing 1*H*-indenes in good to excellent yields. The metallo-radical catalyzed indene synthesis in this paper represents a unique example of a net (formal) intramolecular carbene insertion reaction into a vinylic C(sp²)–H bond, made possible by a controlled radical ring-closure process of the carbene radical intermediate involved. The mechanism was investigated computationally, and the results were confirmed by a series of supporting experimental reactions. Density functional theory calculations reveal a stepwise process involving activation of the diazo compound leading to formation of a Co^{III}-carbene radical, followed by radical ring-closure to produce an indanyl/benzyl radical intermediate. Subsequent indene product elimination involving a 1,2-hydrogen transfer step regenerates the catalyst. Trapping experiments using 2,2,6,6-tetra-methylpiperidine-1-oxyl (TEMPO) radical or dibenzoylperoxide (DBPO) confirm the involvement of cobalt(III) carbene radical intermediates. Electron paramagnetic resonance spectroscopic spin-trapping experiments using phenyl *N*-*tert*-butylnitron (PBN) reveal the radical nature of the reaction.



The mechanism was investigated computationally, and the results were confirmed by a series of supporting experimental reactions. Density functional theory calculations reveal a stepwise process involving activation of the diazo compound leading to formation of a Co^{III}-carbene radical, followed by radical ring-closure to produce an indanyl/benzyl radical intermediate. Subsequent indene product elimination involving a 1,2-hydrogen transfer step regenerates the catalyst. Trapping experiments using 2,2,6,6-tetra-methylpiperidine-1-oxyl (TEMPO) radical or dibenzoylperoxide (DBPO) confirm the involvement of cobalt(III) carbene radical intermediates. Electron paramagnetic resonance spectroscopic spin-trapping experiments using phenyl *N*-*tert*-butylnitron (PBN) reveal the radical nature of the reaction.

INTRODUCTION

Substituted indenes and their closely related indane derivatives are important structural motifs found in many natural products such as taiwaniaquinol,¹ cyanosporaside A/B,² biological active molecules such as endothelin receptors antagonist enrasentan,³ an antipruritic dimetindene,⁴ melatonin receptor,⁵ anti-inflammatory sulindac,⁶ aldosterone synthase inhibitors,⁷ and antitubercular agents.⁸ Some of them are market-leading drugs and/or key intermediates for the synthesis of natural products, pharmaceuticals and other bioactive compounds, as well as functional materials⁹ and metallocene complexes for olefin polymerization (Figure 1).¹⁰ Because of their importance and usefulness, construction of the indene skeleton has attracted interest of synthetic organic and medicinal chemists for several years. Several synthetic methodologies have been developed over the past years, including intra- and intermolecular cyclization reactions, each with their specific advantages and disadvantages.¹¹ Representative intramolecular reactions include ring expansion of suitably substituted cyclopropanes,¹² Friedel–Crafts cyclization of allyl¹³ and propargyl alcohol derivatives,¹⁴ aromatic 1,3 dienes,¹⁵ and α,β unsaturated ketones.¹⁶ Other methods include oxidative cyclizations,¹⁷ palladium catalyzed intramolecular Heck type couplings,¹⁸ ring-closing metathesis,¹⁹ aromatic C–H bond functionaliza-

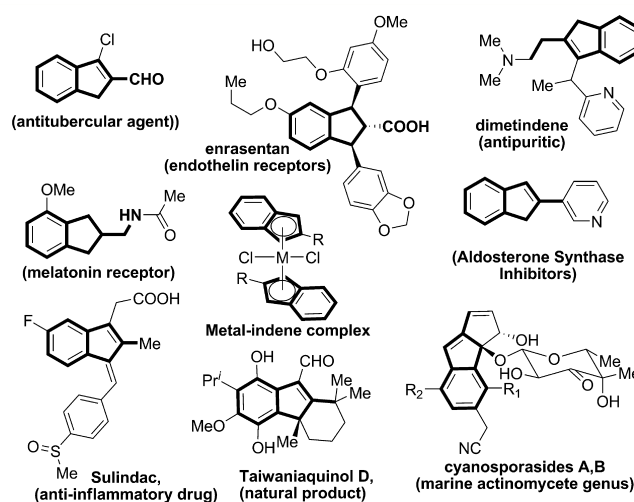


Figure 1. Representative natural products and drug molecules containing indene moieties and some related indane derivatives.

tion,²⁰ intramolecular Morita–Baylis–Hillman approaches,²¹ and gold²² and iodine²³ catalyzed rearrangements.

Received: May 26, 2016

Published: June 24, 2016

A series of intermolecular approaches have also been developed for indene synthesis, including [3 + 2] annulation of aryl alkynes with benzyl derivatives,²⁴ carbonyls,²⁵ allenes and dienophiles,²⁶ palladium-catalyzed carbocyclization of aryl halide/boronic acids and alkynes,²⁷ Fe-catalyzed cyclization of benzyl and substituted alkynes and allenes,²⁸ noble metal catalyzed aromatic C–H bond activation cyclization,²⁹ and copper catalyzed radical cyclizations.³⁰ However, several of these existing methods suffer from functional group intolerance, the necessity of expensive (noble) transition metal catalysts, harsh reaction conditions and/or are limited to the synthesis of specific indenenes with a particular substitution pattern. Hence, in need of a broader pallet of synthetic methodologies the development of new, short, efficient, and broadly applicable catalytic routes to expand the currently available methods for indene synthesis from readily available starting materials is certainly in demand, especially those employing benign, readily available and inexpensive base metal catalysts.

As stable metalloradicals with well-defined open-shell doublet d^7 -electronic configuration, low-spin planar cobalt(II) complexes have recently emerged as a new class of catalysts capable of “carbene-transfer” reactions proceeding via radical mechanisms involving discrete Co^{III} -carbene radical intermediates (Figure 2). Metalloradical activation of carbene precursors

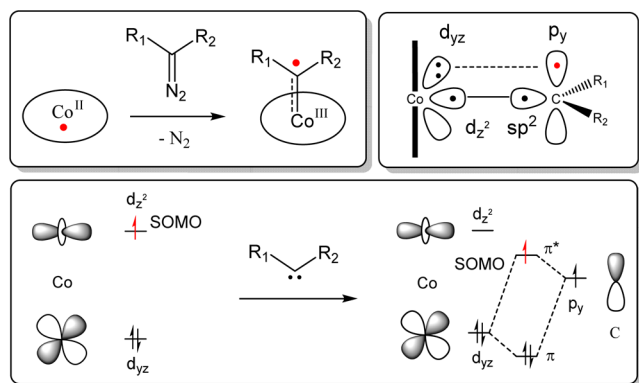


Figure 2. Formation of Co^{III} -carbene radicals (one-electron reduced Fischer-type carbenes) upon reacting planar, low spin cobalt(II) complexes with carbene precursors.

(such as diazo compounds or *N*-tosylhydrazones) produces carbenoids with radical-character at the respective “carbene” carbon, enabling catalytic radical-type organometallic transformations.^{31–36} These carbene-radical intermediates are best described as one-electron reduced Fischer-type carbenes, and as a result they have characteristics of both electrophilic Fischer- and nucleophilic Schrock-type carbenes; besides their radical character they have a reduced tendency to undergo undesirable carbene dimerization reactions.³¹

While the mechanistic details and unusual radical-type electronics of the key carbene radical intermediates were only recently disclosed,³¹ their unique electronic properties have been successfully applied in a variety of interesting metalloradical approaches of synthetic value, including enantioselective alkene cyclopropanation,³² C–H functionalization,³³ β -ester- γ -amino ketones synthesis,³⁴ and in the regioselective synthesis of β -lactams³⁵ and 2*H*-chromenes.³⁶

Herein, we report our efforts to develop a new metalloradical approach for the synthesis of substituted 1*H*-indenenes, taking advantage of the unique reactivity of Co^{III} -carbene radical

intermediates. The method involves a net, overall carbene insertion into a vinylic $\text{C}(\text{sp}^2)\text{--H}$ bond and uses safe and easily accessible *N*-tosyl hydrazones as “carbene” precursors.³⁷ This methodology has a broad substrate scope and can be applied to a variety of aromatic substituted *N*-tosyl hydrazones and conjugated vinyl-groups containing several different functionalities. The cheap and easy to prepare low spin cobalt(II) complex $[\text{Co}^{\text{II}}(\text{MeTAA})]$ (MeTAA = tetramethyltetraaza[14]-annulene) proved to be the most active catalyst among those investigated. Notably, while $[\text{Co}^{\text{II}}(\text{MeTAA})]$ was already synthesized and characterized in 1976,³⁸ it has thus far never been used successfully as a catalyst to the best of our knowledge. Here we report that it has a superior activity over $[\text{Co}(\text{TPP})]$ in catalytic 1*H*-indene synthesis. Furthermore, we disclose a plausible reaction mechanism based on control reactions, radical trapping and deuterium labeling experiments, electron paramagnetic resonance (EPR) spectroscopy and computational studies (density functional theory, DFT).

RESULTS AND DISCUSSION

Our initial attempt to synthesize a substituted 1*H*-indene involved reaction of *o*-cinnamyl *N*-tosyl hydrazone (**1a**) in the presence of the commercially available $[\text{Co}^{\text{II}}(\text{TPP})]$ catalysts (at a temperature of 60 °C, unless indicated otherwise). Different bases such as LiO^tBu , KO^tBu , NaO^tBu , K_2CO_3 , NaOMe (Table 1, entries 1–5) can be used to activate the *N*-tosyl hydrazone in chlorobenzene, but with LiO^tBu the highest yield of the desired 1*H*-indene product **2a** was obtained (51%; entry 1).

Upon increasing the amount of base (LiO^tBu) from 1.2 to 3 equiv the yield dropped substantially (Table 1, entries 1, 6–7).

Table 1. Standardization of Reaction Conditions

entry	catalyst	base	equiv	solvent	yield ^a (%)
1	$[\text{Co}(\text{TPP})]$	LiO^tBu	1.2	PhCl	51
2	$[\text{Co}(\text{TPP})]$	KO^tBu	1.2	PhCl	41
3	$[\text{Co}(\text{TPP})]$	NaO^tBu	1.2	PhCl	36
4	$[\text{Co}(\text{TPP})]$	K_2CO_3	1.2	PhCl	39
5	$[\text{Co}(\text{TPP})]$	NaOMe	1.2	PhCl	27
6	$[\text{Co}(\text{TPP})]$	LiO^tBu	2	PhCl	32
7	$[\text{Co}(\text{TPP})]$	LiO^tBu	3	PhCl	0
8	$[\text{Co}(\text{TPP}-\text{F}_{20})]$	LiO^tBu	1.2	toluene	0
9	$[\text{Co}(\text{MeTAA})]$	LiO^tBu	1.2	toluene	83
10	$[\text{Co}(\text{salen})]$	LiO^tBu	1.2	toluene	00
11	$[\text{CuI}]$	LiO^tBu	1.2	toluene	27
12	$[\text{Rh}_2(\text{OAc})_4]$	LiO^tBu	1.2	toluene	0
13	$[\text{Co}(\text{MeTAA})]$	LiO^tBu	1.2	PhCl	78
14	$[\text{Co}(\text{MeTAA})]$	LiO^tBu	1.2	PhH	86
15	$[\text{Co}(\text{MeTAA})]$	LiO^tBu	1.2	THF	85
16	$[\text{Co}(\text{MeTAA})]$	LiO^tBu	1.2	CH_2Cl_2	46
17	$[\text{Co}(\text{MeTAA})]$	LiO^tBu	1.2	CH_3CN	55
18	$[\text{Co}(\text{MeTAA})]$	LiO^tBu	1.2	hexane	70
19	–	LiO^tBu	1.2	PhH	0
20 ^b	$[\text{Co}(\text{MeTAA})]$	LiO^tBu	1.2	PhH	35

^aYields were determined by integration of the ^1H NMR signals in the presence of acenaphthene as internal standard. ^bReaction carried out at room temperature.

This is probably caused by decomposition or poisoning of the catalyst in the presence of excess base. To improve the yield of the reaction different cobalt(II) sources were investigated. The fluorinated porphyrin and salen based cobalt catalysts (Table 1, entry 8, 10) did not produce the desired product, but the cheap and easy to prepare $[\text{Co}^{\text{II}}(\text{MeTAA})]$ catalyst (Figure 2) produced 1*H*-indene **2a** in excellent yield (83%) using toluene as the solvent (Table 1, entry 9).

$[\text{Co}^{\text{II}}(\text{MeTAA})]$ is the cobalt(II) complex of the tetramethyltetraaza[14]annulene (MeTAA) ligand (Figure 3).

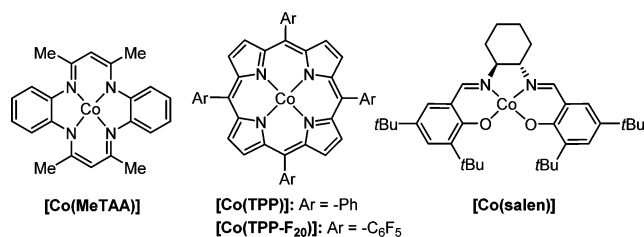


Figure 3. Structures of the cobalt(II) catalysts used in this study.

The complex was first prepared in 1976,³⁸ involving two simple steps to obtain the complex in near quantitative yield. This is in sharp contrast to the synthesis of porphyrin complexes, which is in general work-intensive, low yielding, time-consuming and produces large amounts of unwanted side products, thus demanding elaborate (column chromatographic) purification steps. The MeTAA ligand has similar bonding properties as a porphyrin, which reflects in its ability to bind a variety of transition metals.^{39,40} However, there are also some differences which likely explain its increased reactivity as compared to $[\text{Co}(\text{TPP})]$. While porphyrins have an aromatic ($4n + 2$) delocalized π -cloud, MeTAA is Hückel antiaromatic ($4n$), which increases the flexibility of the ligand. Another difference between these two macrocyclic structures is their ring size (14- vs 16-membered ring). The increased flexibility and smaller ring-size of MeTAA as compared to a porphyrin leads to deviation from planarity, and as such $[\text{Co}^{\text{II}}(\text{MeTAA})]$ adopts a saddle shaped configuration.

Other catalysts such as $[\text{CuI}]$ or $[\text{Rh}_2(\text{OAc})_4]$ (Table 1, entries 11–12) proved less or not effective. Quite surprisingly the carbene transfer catalyst $[\text{Rh}_2(\text{OAc})_4]$, which is well-known to be operative in a variety of carbene C–H bond insertion reactions,⁴¹ produced no indene at all. In general, carbene insertion into vinylic $\text{C}(\text{sp}^2)\text{--H}$ bonds is extremely rare if not entirely unprecedented, likely because cyclopropanation is favored for other (nonmetalloradical) carbene transfer catalysts. Notably, however, CuI did catalyze the reaction to some extent but produced only 27% of the desired indene, with mainly the carbene–carbene dimerized product being formed in the undesired side reaction.

Extended solvent screening revealed that the reaction works best in nonpolar solvents such as benzene, toluene, or hexane (entries 9, 14, 18). Most polar solvents such as CH_2Cl_2 or CH_3CN (entries 16–17) led to comparatively low yields, but THF works well as a solvent (entry 15). The reaction does not produce **2a** without a catalyst (entry 19), and the yield of the reaction drops drastically when performing the reaction at room temperature (entry 20). Conversion of the *N*-tosyl hydrazone into the corresponding diazo compound accounts for at least part of the required activation energy.³⁷

To explore the scope of the metalloradical catalyzed indene synthesis, several different functional groups were introduced at the vinylic double bond (Table 2). Several α,β -unsaturated

Table 2. Substrates Scope Varying Functional Groups at the Vinylic Double Bond^a

Entry	R-	Products	Yield ^b (%)
1	-COOMe (1a)	(2a)	86
2	-COOEt (1b)	(2b)	78
3	-COO ⁿ Bu (1c)	(2c)	80
4	-COO ^t Bu (1d)	(2d)	76
5	-COOPh (1e)	(2e)	82
6	-CONMe ₂ (1f)	(2f)	98
7	-CN (1g)	(2g)	52
8	-Ph (1h)	(2h)	85

^aReaction conditions: *N*-tosylhydrazone (**1a–h**) (0.2 mmol, 1.0 equiv), LiO^tBu (0.24 mmol, 1.2 equiv), $[\text{Co}(\text{MeTAA})]$ (5 mol %), benzene (3 mL), 60 °C, overnight. ^bIsolated yields after column chromatography.

esters are tolerated (i.e., the Et-, *n*Bu-, *t*Bu-, and Ph-esters **1a–e**), producing indenenes **2a–e** in good to excellent yields (78–86%, entries 1–5) using the standardized reaction conditions shown in Table 2. Surprisingly, α,β -unsaturated amide **1f** produced indene **2f** in even higher yield (98%; entry 6), and also styrene derivative **1h** furnished the corresponding indene product **2h** in good yield (85%; entry 8). The α,β -unsaturated nitrile substrate **1g** works less well, producing indene **2g** in moderate yield (52%; entry 7).

The substrate scope was further explored and broadened by investigating the effect of varying the substituents on the aromatic ring (Table 3). Substitution at the 5- or 6- position of the aromatic ring does not affect the yield of the products **2i** (Table 3, entries 1–2). Electron withdrawing substituents such as -F, -Cl, -CF₃, and -NO₂ are all effective, affording the corresponding indenenes **2i–l** in good to excellent yields (Table 3, entries 1–5). Reactions proceeded even better with neutral electron-donating groups on the aromatic ring such as naphthyl (**1n**) and methyl (**1o**) groups producing the corresponding indenenes **2m,n** in excellent yields (Table 3, entries 6–7). Substrates **1p,q** bearing 5-methoxy and 4,5-dimethoxy substituents produced indenenes **2o,p** in a somewhat lower yield (~70%).

For most of the asymmetrically substituted substrates shown in Table 3 (except entry 10) both possible regio-isomers of products **2i–p** are formed in a nearly 1:1 ratio. This points to allylic/benzylic double bond isomerization under the applied reaction conditions, as can be expected for 1*H*-indenenes having rather acidic allylic/benzylic protons. Substitution at the allylic/benzylic position has also been investigated. Interestingly

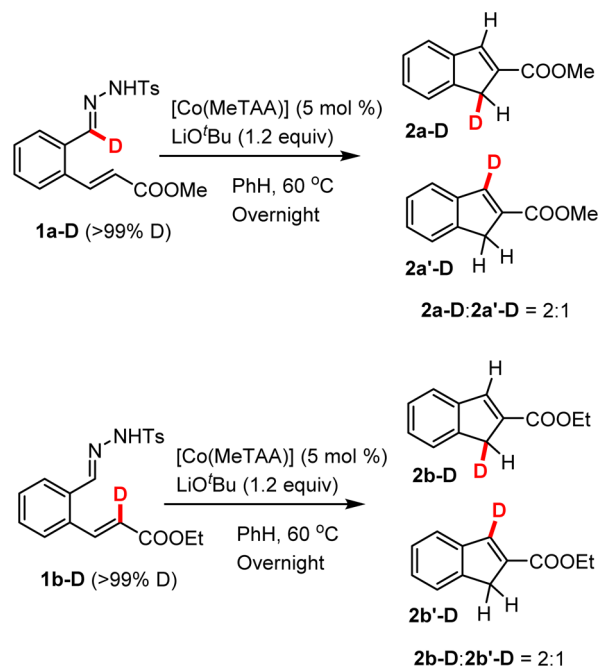
Table 3. Substrates Scope Bearing Various Functional Group on Aromatic Ring^a

Entry	Substrates	Products	Yield (%) ^b
1	(1i)	(2i)	87 ^c
2	(1j)	(2i)	85 ^c
3	(1k)	(2j)	82 ^c
4	(1l)	(2k)	84 ^c
5	(1m)	(2l)	84 ^c
6	(1n)	(2m)	93 ^c
7	(1o)	(2n)	88 ^c
8	(1p)	(2o)	72 ^c
9	(1q)	(2p)	70
10	(1s)	(3)	95

^aReaction conditions: *N*-tosylhydrazone (**1i–s**) (0.2 mmol, 1.0 equiv), LiO^tBu (0.24 mmol, 1.2 equiv), CoMeTAA (5 mol %), benzene (3 mL), 60 °C, overnight. ^bIsolated yields after column chromatography. ^cNearly 1:1 ratio of both isomers formed.

reacting *N*-tosylhydrazone **1s** results in regioselective formation of indene product **3** in high yield (Table 3, entry 10) with the double bond at the thermodynamically favored most substituted position.

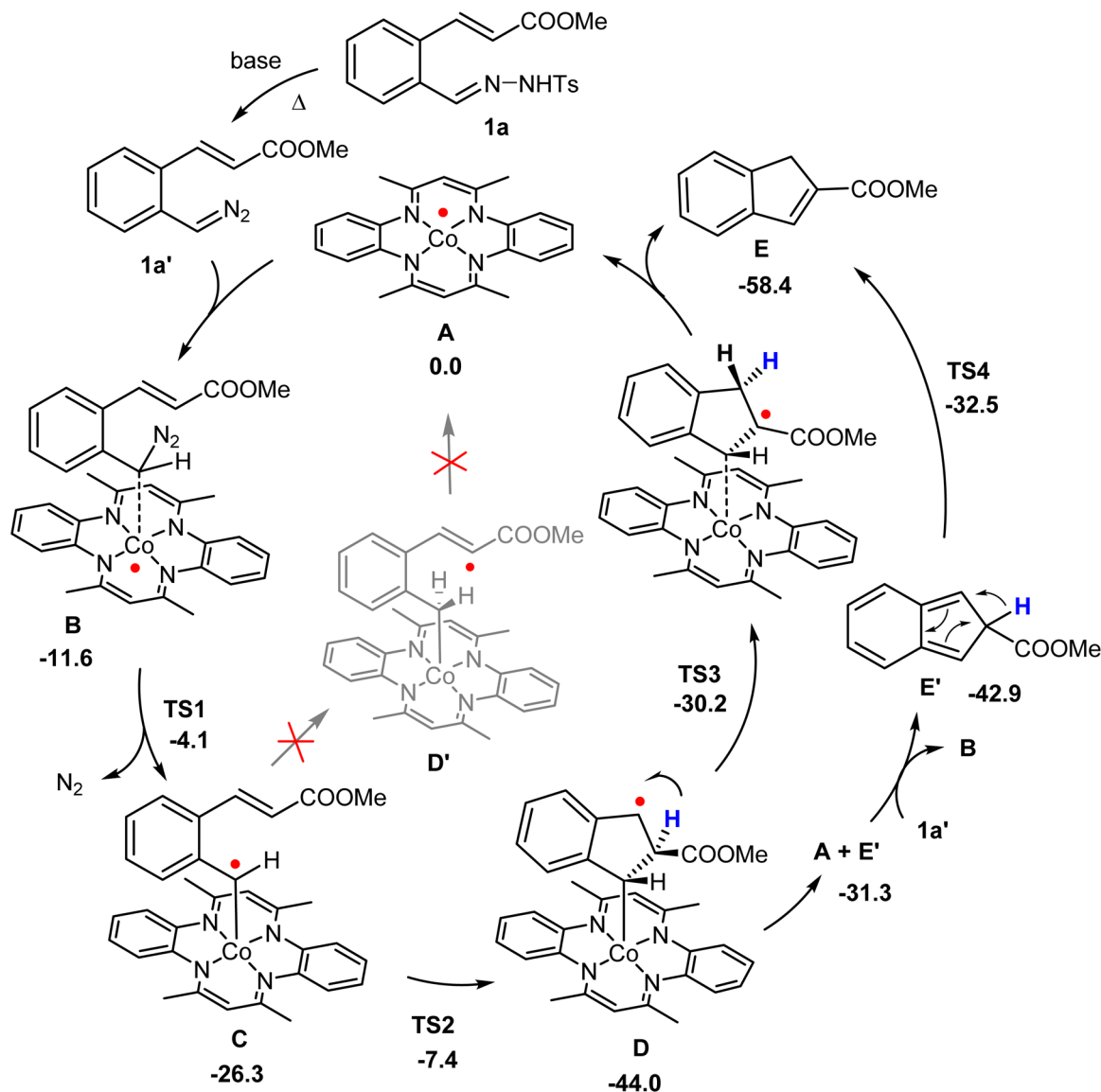
Full statistical (thermodynamically controlled) scrambling of the allylic and vinylic protons under the applied (alkaline) reaction conditions was confirmed by the deuterium-labeling experiments shown in Scheme 1. Starting either with a

Scheme 1. Deuterium-Labeling Experiments Showing Complete Scrambling of Allylic and Vinylic Protons

deuterium label at the azomethine position (**1a-D**) or at the vinylic position (**1b-D**) of the carbenoid precursor leads in both cases to a complete statistical distribution of the deuterium atoms over the allylic/benzylic and vinylic positions, as indicated by a 2:1 ratio of the –CDH– and =CD signals in the D-NMR spectra of deuterium-labeled indene products **2a-D/2a'-D** and **2b-D/2b'-D** (Scheme 1).

To shed more light on the catalytic reaction mechanism, we explored the mechanism computationally. Additionally we performed a set of trapping and control experiments, combined with EPR spectroscopic investigations.

At first sight the reaction may seem to proceed via a direct carbene insertion into the vinylic C(sp²)–H bond. However, such reactions are unprecedented to the best of our knowledge, and [Rh₂(OAc)₄] (which is well-known for its reactivity in aromatic and aliphatic C–H bond functionalization by direct carbene insertion) is not active in 1*H*-indene formation (vide supra). In addition, attempts to find a transition state for this process for the [Co(MeTAA)] catalyst with DFT were unsuccessful, and the electronic structure of a Co^{III}-carbene radical in general (Figure 2) seems to be incompatible with any direct, concerted C–H insertion mechanism of the carbenoid. Hydrogen atom transfer from the vinylic C–H bond to the carbene radical followed by a radical rebound step could in principle be an alternative, but all attempts to optimize such a vinyl radical intermediate (**D'** in Scheme 2) converged back to carbene radical **C**, thus indicating that the route via **D'** is not a viable pathway. As such, a metalloradical pathway involving

Scheme 2. Proposed Mechanism of [Co(MeTAA)] Catalyzed 1*H*-Indene Synthesis^a

^aDFT-D3 calculated (Turbomole, BP86, def2-TZVP, disp3) mechanism for [Co(MeTAA)] catalyzed 1*H*-indene formation (free energies, $\Delta G_{298\text{K}}^\circ$, in kcal mol⁻¹). All energies, including the transition states, are reported with respect to species A as the reference point.

attack of the carbene radical at the vinylic double bond to form the cyclized γ -radical intermediate D seems to be the most plausible mechanism. This mechanism was fully explored for both the [Co(MeTAA)] and [Co(TPP)] catalysts with DFT-D3 at the BP86, def2-TZVP level, using Grimme's version dispersion corrections (disp3). The selected computational method is in agreement with our previous studies involving Co(III)-carbene radicals as intermediates in catalytic cyclizations, and is known to provide accurate Co–C BDEs.⁴²

The computed mechanism for the [Co(MeTAA)] catalyst is presented in Scheme 2. The corresponding mechanism for the [Co(TPP)] catalyst and the associated energy diagrams of the reactions with both catalysts are shown in the Supporting Information (Figure S1). All steps have accessible barriers, and each step is exergonic.

The first steps of the DFT computed reaction mechanism involve trapping and activation of the in situ generated diazo compound by the [Co(MeTAA)] catalyst (Scheme 2). Formation of the Co^{II}-catalyst-diazo adduct B is exergonic

($\Delta G^\circ = -11.6$ kcal mol⁻¹), as is N₂-elimination from B to produce the Co^{III}-carbene radical species C ($\Delta G^\circ = -14.7$ kcal mol⁻¹). The transition state barrier for formation of C from B is low (TS1; $\Delta G^\ddagger = +7.4$ kcal mol⁻¹). These steps are similar to those reported previously in the mechanisms for 2*H*-chromene formation³⁶ and cyclopropanation³¹ using Co^{II}-porphyrin catalysts.

The next step involves addition of the carbene radical to the vinylic double bond producing the cyclized γ -radical intermediate D ($\Delta G^\circ = -17.7$ kcal mol⁻¹) via transition state TS2 (barrier: $\Delta G^\ddagger = +18.9$ kcal mol⁻¹). This appears to be the rate limiting step of the catalytic cycle. Indene formation from D requires a low barrier 1,2-hydrogen atom transfer (TS3; $\Delta G^\ddagger = +13.8$ kcal mol⁻¹), relocating the radical from the γ - to the β -position. The thus formed cobalt-bound β -radical species is so unstable that it spontaneously dissociates in a barrierless manner to form indene product E. The overall process is strongly exergonic ($\Delta G^\circ = -58.4$ kcal mol⁻¹).

An alternative pathway for indene formation from **D** is possible, involving dissociation of the dearomatized (methide-like 2*H*-indene) **E'** from **D**, followed by 1,2 hydride shift (**TS4**) to produce the 1*H*-indene product **E** (**Scheme 2**). Dissociation of **E'** from **D** involving homolytic splitting of the Co–C bond to produce starting complex **A** is endergonic by about +13 kcal mol⁻¹ according to DFT (the reverse reaction is barrierless), but coordination of substrate **1a'** to **A** producing **B** makes the overall process virtually thermoneutral. Subsequent conversion of **E'** to **E** has a low barrier transition state (**TS4**; $\Delta G^\ddagger = +10.4$ kcal mol⁻¹). The computed pathways for indene formation from **D** via **E'** ($\Delta G^\ddagger = +12.7$ kcal mol⁻¹; determined by dissociation of **E'** to form **A**) and the direct pathway over **TS3** ($\Delta G^\ddagger = +13.8$ kcal mol⁻¹) have very similar overall barriers, and thus seem to be competing trails producing the same product.

Spin density plots of the key intermediates **C** and **D** are presented in **Figure 4**. Most spin density is ligand centered for

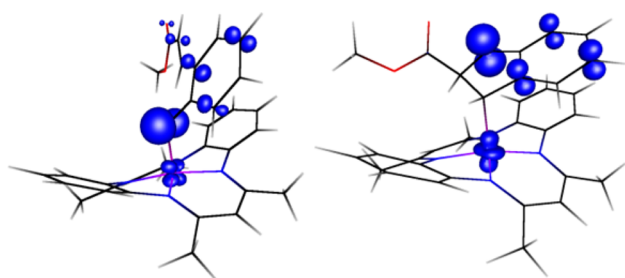


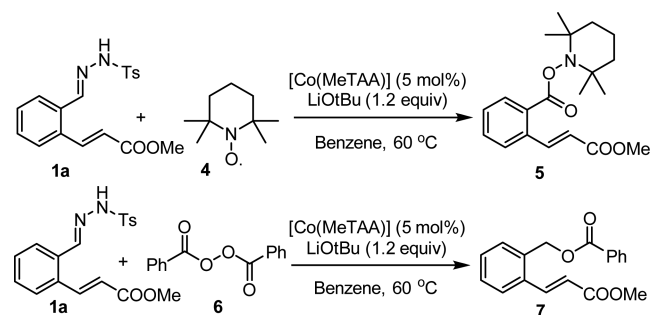
Figure 4. (a) Spin density plots of the DFT-optimized Co^{III}-carbene radical species **C** (left) and cyclized γ -radical intermediate **D** (right).

both intermediates. For intermediate **C** the highest spin population is found on the carbenoid carbon atom, in agreement with a Co^{III}-carbene radical electronic structure as presented in **Figure 2**. In intermediate **D** the largest spin population is found at the γ -position, with some delocalization over the adjacent phenyl moiety. Both structures have less than 10% spin population at cobalt, thus showing that radical-type elementary steps involving coordinated substrate radicals play a key role in the catalytic mechanism.

To obtain additional information about the mechanistic pathway we attempted to trap intermediates with radical scavengers.⁴³ In agreement with the above DFT calculations indicating that Co^{III}-carbene radical intermediate **C** is the catalytic resting state, these trapping experiments produced in all cases products stemming from species **C** (**Scheme 3**).

Reacting substrate **1a** with [Co(MeTAA)] in the presence of three equivalents of TEMPO under identical reaction

Scheme 3. Radical Scavenging Experiments Used to Trap the Co^{III}-Carbene Radical Intermediate



conditions as used in catalytic indene synthesis led to formation of product **5** (**Scheme 3**). Compound **5** was isolated, purified by column chromatography and characterized by ¹H, ¹³C and GCMS spectroscopy (see **Supporting Information**). The compound has a TEMPO moiety attached to the carbon stemming from the “carbene”, which is (over)oxidized to a carbonyl group. The use of dibenzoylperoxide as a radical-scavenger also led to trapping of carbene radical intermediate **C**, in this case leading to formation of product **7** (**Scheme 3**). No ring-closed intermediates could be trapped, consistent with **TS2** being the rate limiting step in the DFT calculated mechanism with all follow-up steps after formation of **D** being fast (**Scheme 1**). Cold spray electron spray ionization high resolution mass spectrometry (ESI-HRMS) experiments of the catalytic reaction mixture in absence of radical scavengers are in agreement with the presence of carbenoid species **C** (**Scheme 2**). The detected mass $m/z = 576.1906$ (calc. $m/z = 576.1936$) corresponds to [C+H]⁺ (C₃₃H₃₃CoN₄O₂), and can be attributed to protonated species **C**.

Spin trapping experiments using phenyl *N*-*tert*-butylnitron (PBN) as the spin trap support the proposed radical-type mechanism. Heating a mixture of **1a**, [Co(MeTAA)], LiOtBu in the presence of PBN led to formation of PBN-trapped carbon-centered radicals as detected with EPR spectroscopy (**Figure 5**).

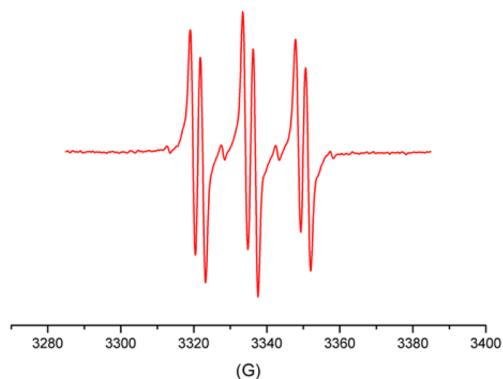


Figure 5. Isotropic X-band EPR spectrum of the PBN-trapped carbon-centered radical ($T = 298$ K; microwave frequency: 9.36607 GHz; power: 6.33 mW; modulation amplitude: 1.0 G).

The resulting EPR signal ($g = 2.0063$, $A_N = 14.4$ G, $A_H = 2.8$ G) is strong and similar to other reported PBN-trapped carbon centered radicals.⁴⁴ Heating the reaction mixture in absence of cobalt (i.e., noncatalytic conditions, in which case no indene formation occurs) also some PBN-trapped radicals were detectable, but different ones with weaker intensity (see **Supporting Information**).

CONCLUSIONS

Metalloradical activation of a series of *o*-cinnamyl-*N*-tosyl hydrazones produces a variety of functionalized 1*H*-indenes in high yields and with a broad functional group tolerance. The reaction uses readily available starting materials and is operationally simple, thus representing a practical method for the construction of substituted 1*H*-indene derivatives. The cheap and easy to prepare low spin cobalt(II) complex [Co(MeTAA)] proved to be the most active catalyst among those investigated, showcasing for the first time catalytic activity of this complex in general. DFT studies reveal a stepwise process involving activation of the diazo compound leading

formation of a Co^{III}-carbene radical, followed by a rate limiting radical ring-closure step to produce an indanyl-radical intermediate. Subsequent 1,2-hydrogen atom transfer leads to elimination of the 1*H* indene product and regenerates the Co^{II}-catalyst. The computed mechanism was confirmed by a series of supporting radical-scavenging experiments. Deuterium labeling experiments further reveal statistical scrambling of the allylic/benzylic and vinylic protons under the applied reaction conditions. The metallo-radical catalyzed indene synthesis in this paper represents a rare example of a net, formal (intramolecular) carbene insertion reaction into a vinylic C(sp²)-H bond, made possible by taking advantage of the distinctive and controlled reactivity of the key Co^{III}-carbene radical intermediates involved. Further studies aimed at exploring the controlled organometallic radical-type reactivity of transition metal carbene radicals in ring-closing reactions and C-H bond functionalization are underway.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05434.

Compound characterization data (NMR, HRMS, etc.), absolute energies (atomic units), coordinates of the DFT-optimized structures (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*b.debruijn@uva.nl

Author Contributions

†BGD and AC contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Ed Zuidinga for MS measurements, Jan Meine Ernsting for NMR advice and Tim Storr for providing [Co(salen)]. Financial support from The Netherlands Organization for Scientific Research (NWO-CW VICI project 016.122.613) and the University of Amsterdam (Research Priority Area Sustainable Chemistry) is gratefully acknowledged.

■ REFERENCES

- (1) (a) Deng, J.; Zhou, S.; Zhang, W.; Li, J.; Li, R.; Li, A. *J. Am. Chem. Soc.* **2014**, *136*, 8185. (b) Chang, C.; Chien, S.-C.; Lee, S.; Kuo, Y.-H. *Chem. Pharm. Bull.* **2003**, *51*, 1420.
- (2) (a) Yamada, K.; Lear, M. J.; Yamaguchi, T.; Yamashita, S.; Gridnev, I. D.; Hayashi, Y.; Hiram, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 13902. (b) Lane, A. L.; Nam, S.-J.; Fukuda, T.; Yamanaka, K.; Kauffman, C. A.; Jensen, P. R.; Fenical, W.; Moore, B. S. *J. Am. Chem. Soc.* **2013**, *135*, 4171. (c) Jensen, P. R.; Williams, P. G.; Oh, D.-C.; Zeigler, L.; Fenical, W. *Appl. Environ. Microbiol.* **2007**, *73*, 1146.
- (3) (a) Alessandro, C. *Cardiovasc. Drug Rev.* **2003**, *21*, 1. (b) Underwood, D. C.; Bochnowicz, S.; Osborn, R. R.; Luttmann, M. A.; Hay, D. W. *J. Pharm. Exp. Ther.* **1997**, *283*, 1130.
- (4) (a) Douros, A.; Bronder, E.; Andersohn, F.; Klimpel, A.; Thomae, M.; Sarganas, G.; Kreutz, R.; Garbe, E. *Br. J. Clin. Pharmacol.* **2015**, *79*, 988. (b) Hefner, G.; Stieffenhofer, V.; Gabriel, S.; Palmer, G.; Mueller, K.-M.; Roeschke, J.; Hiemke, C. *Eur. J. Clin. Pharmacol.* **2015**, *71*, 165.
- (5) (a) Mor, M.; Rivara, S.; Silva, C.; Bordi, F.; Plazzi, P. V.; Spadoni, G.; Diamantini, G.; Balsamini, C.; Tarzia, G.; Frascini, F. *J. Med. Chem.* **1998**, *41*, 3831. (b) Hardeland, R. *Curr. Pharm. Des.* **2016**, *22*, 1086.

- (6) (a) Femia, A. P.; Soares, P. V.; Luceri, C.; Lodovici, M.; Giannini, A.; Caderni, G. *BMC Cancer* **2015**, *15*, 1. (b) Prade, E.; Barucker, C.; Sarkar, R.; Althoff-Ospelt, G.; Lopez, D. A.; Juan, M.; Hossain, S.; Zhong, Y.; Multhaup, G.; Reif, B. *Biochemistry* **2016**, *55*, 1839. (c) Raz, A. *Biochem. Pharmacol.* **2002**, *63*, 343.
- (7) Voets, M.; Antes, I.; Scherer, C.; Vieira, U. M.; Biemel, K.; Oberwinkler, S. M.; Hartmann, R. W. *J. Med. Chem.* **2006**, *49*, 2222.
- (8) (a) Kahlon, A. K.; Negi, A. S.; Kumari, R.; Srivastava, K. K.; Kumar, S.; Darokar, M. P.; Sharma, A. *Appl. Microbiol. Biotechnol.* **2014**, *98*, 2041. (b) Chandab, D.; Saikiab, D.; Kumarc, J. K.; Thakurb, J. P.; Agarwalb, J.; Chanotiyaa, C. S.; Shankera, K.; Negi, A. S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3966.
- (9) (a) Grimsdale, A. C.; Mullen, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 5592. (b) Zhu, X.; Tsuji, H.; Nakabayashi, K.; Ohkoshi, S.-I.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 16342. (c) Hu, P.; Lee, S.; Herng, T. S.; Aratani, N.; Gonçalves, T. P.; Qi, Q.; Shi, X.; Yamada, H.; Huang, K.-W.; Ding, J.; Kim, D.; Wu, J. *J. Am. Chem. Soc.* **2016**, *138*, 1065.
- (10) (a) Alt, H. G.; Koppl, A. *Chem. Rev.* **2000**, *100*, 1205. (b) Ren, S.; Igarashi, E.; Nakajima, K.; Kanno, K.; Takahashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 7492. (c) Zargarian, D. *Coord. Chem. Rev.* **2002**, *233*, 157. (d) Leino, R.; Lehmus, P.; Lehtonen, A. *Eur. J. Inorg. Chem.* **2004**, *2004*, 3201.
- (11) Reviews: (a) Ivchenko, N. B.; Ivchenko, P. V.; Nifant'ev, I. E. *Russ. J. Org. Chem.* **2000**, *36*, 609. (b) Enders, M.; Baker, R. W. *Curr. Org. Chem.* **2006**, *10*, 937. (c) Gabriele, B.; Mancuso, R.; Veltri, L. *Chem. - Eur. J.* **2016**, *22*, 5056.
- (12) (b) Zhu, Z.-B.; Shi, M. *Chem. - Eur. J.* **2008**, *14*, 10219. (c) Wang, Y.; Liao, W.; Huang, G.; Xia, Y.; Yu, Z.-X. *J. Org. Chem.* **2014**, *79*, 5684. (e) Bahadur, K.; Magar, S.; Lee, Y. R. *Org. Lett.* **2013**, *15*, 4288.
- (13) (a) Shanmugam, P.; Rajasingh, P. *Chem. Lett.* **2005**, *34*, 1494. (b) Dethe, D. H.; Murhade, G. *Org. Lett.* **2013**, *15*, 429. (c) Zhang, X.; Teo, W. T.; Rao, W.; Ma, D.-L.; Leung, C.-H.; Chan, P. W. H. *Tetrahedron Lett.* **2014**, *55*, 3881.
- (14) (a) Sousa, C. M.; Berthet, J.; Delbaere, S.; Coelho, P. J. *J. Org. Chem.* **2014**, *79*, 5781. (b) Egi, M.; Shimizu, K.; Kamiya, M.; Ota, Y.; Akai, S. *Chem. Commun.* **2015**, *51*, 380. (c) Prasad, B. A. B.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468.
- (15) Eom, D.; Park, S.; Park, Y.; Ryu, T.; Lee, P. H. *Org. Lett.* **2012**, *14*, 5392.
- (16) (a) Boblak, K. N.; Klumpp, D. A. *J. Org. Chem.* **2014**, *79*, 5852. (b) Kheira, H.; Li, P.; Xu, J. *J. Mol. Catal. A: Chem.* **2014**, *391*, 168. (c) Dethe, D. H.; Murhade, G. M. *Chem. Commun.* **2013**, *49*, 8051.
- (17) Wang, H.; Zhao, Y.-L.; Li, L.; Li, S.-S.; Liu, Q. *Adv. Synth. Catal.* **2014**, *356*, 3157.
- (18) (a) Shao, J.; Hu, P.; Hong, G.; Fang, M.; Li, X.; Xu, X. *Synlett* **2014**, *25*, 1009. (b) Zhou, F.; Han, X.; Lu, X. *J. Org. Chem.* **2011**, *76*, 1491.
- (19) (a) Coyanis, M.; Panayides, J.-L.; Fernandes, M. A.; de Koning, C. B.; van Otterlo, W. A. L. *J. Organomet. Chem.* **2006**, *691*, 5222. (b) Calder, E. D. D.; McGonagle, F. I.; Harkiss, A. H.; McGonagle, G. A.; Sutherland, A. *J. Org. Chem.* **2014**, *79*, 7633.
- (20) (a) Tobisu, M.; Nakai, H.; Chatani, N. *J. Org. Chem.* **2009**, *74*, 5471. (b) Yang, S.; Li, Z.; Jian, X.; He, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 3999.
- (21) Nagarajan, S.; Muthuvel, P.; Das, T. M. *Synlett* **2011**, *2011*, 2163.
- (22) (a) Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 31. (b) Hashmi, A. S. K.; Braun, I.; Nosel, P.; Schadlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 4456. (c) Sanz, R.; Miguel, D.; Rodriguez, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7354. (d) Corma, A.; Leyva-Perez, A.; Sabater, M. *Chem. Rev.* **2011**, *111*, 1657. (e) Zi, W.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 12600. (f) Li, C.; Zeng, Y.; Wang, J. *Tetrahedron Lett.* **2009**, *50*, 2956.
- (23) (a) Wang, X.-C.; Zhonga, M.-J.; Liang, Y.-M. *Org. Biomol. Chem.* **2012**, *10*, 3636. (b) Khan, Z. A.; Wirth, T. *Org. Lett.* **2009**, *11*, 229.

- (24) (a) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202. (b) Bu, X.; Hong, J.; Zhou, X. *Adv. Synth. Catal.* **2011**, *353*, 2111. (c) Chen, Y.; Li, K.; Liu, X.; Zhu, J.; Chen, B. *Synlett* **2013**, *24*, 130.
- (25) Obora, Y.; Kimura, M.; Tokunaga, M.; Tsuji, Y. *Chem. Commun.* **2005**, 901.
- (26) (a) Yamazaki, S.; Yamamoto, Y.; Fukushima, Y.; Tabayashi, M.; Ukai, T.; Mikata, Y. *J. Org. Chem.* **2010**, *75*, 5216. (b) Yamakazi, S.; Fukushima, Y.; Ukai, T.; Tatsumi, K.; Ogawa, A. *Synthesis* **2012**, *44*, 2155.
- (27) (a) Jia, X.; Petrone, D. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9870. (b) Zhu, X.; Mitsui, C.; Tsuji, H.; Nakamura, E. *J. Am. Chem. Soc.* **2009**, *131*, 13596. (c) Zhou, F.; Yang, M.; Lu, X. *Org. Lett.* **2009**, *11*, 1405.
- (28) (a) Chen, Y.; Li, K.; Liu, X.; Zhu, J.; Chen, B. *Synlett* **2013**, *24*, 130. (b) Liu, C.-R.; Wang, T.-T.; Qi, Q.-B.; Tian, S.-K. *Chem. Commun.* **2012**, *48*, 10913.
- (29) (a) Muralirajan, K.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 4169. (b) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202. (c) Huang, X.-C.; Yang, X.-H.; Song, R.-J.; Li, J.-H. *J. Org. Chem.* **2014**, *79*, 1025.
- (30) (a) Zhang, D.; Liu, Z.; Yum, E. K.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 251. (b) Zeng, X.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 17638.
- (31) (a) Dzik, W. I.; Xu, X.; Zhang, X. P.; Reek, J. N. H.; de Bruin, B. *J. Am. Chem. Soc.* **2010**, *132*, 10891. (b) Lu, H.; Dzik, W. I.; Xu, X.; Wojtas, L.; de Bruin, B.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 8518. (c) Dzik, W. I.; Zhang, X. P.; de Bruin, B. *Inorg. Chem.* **2011**, *50*, 9896. (d) Dzik, W. I.; Reek, J. N. H.; de Bruin, B. *Chem. - Eur. J.* **2008**, *14*, 7594. (e) Lyaskovskyy, V.; de Bruin, B. *ACS Catal.* **2012**, *2*, 270.
- (32) (a) Doyle, M. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 850. (b) Zhu, S. F.; Ruppel, J. V.; Lu, H. J.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2008**, *130*, 5042. (c) Zhu, S. F.; Perman, J. A.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8460. (d) Fantauzzi, S.; Gallo, E.; Rose, E.; Raoul, N.; Caselli, A.; Issa, S.; Ragaini, F.; Cenini, S. *Organometallics* **2008**, *27*, 6143. (e) Xu, X.; Zhu, S.; Cui, X.; Wojtas, L.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 11857.
- (33) (a) Ruppel, J. V.; Kamble, R. M.; Zhang, X. P. *Org. Lett.* **2007**, *9*, 4889. (b) Lu, H.-J.; Li, C.-Q.; Jiang, H.-L.; Lizardi, C. L.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 7028.
- (34) Zhang, J.; Jiang, J.; Xu, D.; Luo, Q.; Wang, H.; Chen, J.; Li, H.; Wang, Y.; Wan, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 1231.
- (35) Paul, N. D.; Chirila, A.; Lu, H.; Zhang, X. P.; de Bruin, B. *Chem. - Eur. J.* **2013**, *19*, 12953.
- (36) Paul, N. D.; Mandal, S.; Otte, M.; Cui, X.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2014**, *136*, 1090.
- (37) (a) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735. (b) Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486. (c) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560. (d) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236. (e) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 775. (f) Hu, F.; Xia, Y.; Ye, F.; Liu, Z.; Ma, C.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1364.
- (38) Weiss, M. C.; Goedken, V. L. *J. Am. Chem. Soc.* **1976**, *98*, 3389.
- (39) (a) Mountford, P. *Chem. Soc. Rev.* **1998**, *27*, 105. (b) Cotton, F. A.; Czuchajowska, J. *Polyhedron* **1990**, *9*, 2553.
- (40) Recent examples: (a) Imler, G. H.; Bhagan, S.; Coffin, V. L.; Wayland, B. B. *Inorg. Chem.* **2012**, *51*, 3352. (b) Imler, G. H.; Zdilla, M. J.; Wayland, B. B. *Inorg. Chem.* **2013**, *52*, 11509. (c) Imler, G. H.; Zdilla, M. J.; Wayland, B. B. *J. Am. Chem. Soc.* **2014**, *136*, 5856. (d) Imler, G. H.; Peters, G. M.; Zdilla, M. J.; Wayland, B. B. *Inorg. Chem.* **2015**, *54*, 273.
- (41) (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (b) Davies, H. M. L.; Beckwith, R. E. *J. Chem. Rev.* **2003**, *103*, 2861.
- (42) (a) Li, S.; Peng, C.-H.; Fryd, M.; Wayland, B. B.; de Bruin, B. *J. Am. Chem. Soc.* **2008**, *130*, 13373. (b) de Bruin, B.; Dzik, W. I.; Li, S.; Wayland, B. B. *Chem. - Eur. J.* **2009**, *15*, 4312.
- (43) Lu, H.; Dzik, W. I.; Xu, X.; Wojtas, L.; de Bruin, B.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 8518.
- (44) Buettner, G. R. *Free Radical Biol. Med.* **1987**, *3*, 259.