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Metal-Catalyzed and Metal-Free Intermolecular Amination of Light Alkanes and Benzenes

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1. Introduction

Natural gas processing and crude petroleum refining provide essential saturated and unsaturated hydrocarbons (especially light alkanes, alkenes, and aromatics), which are extensively used as energy-generating fuels and space heating materials, and to a much lesser extent as starting materials for producing commodity chemicals. In the latter function, this valuable feedstock requires initial functionalization (for instance, halogenation, nitrogenation, carbonylation, oxidation/reduction) prior to becoming available for the synthesis of targeted commodity chemicals. Frequently, circuitous synthetic methodologies are employed that are energetically wasteful and environmentally hazardous, as for instance in the synthesis of methanol from initial deep oxidation of methane, followed by reduction of synthesis gas over heterogeneous catalysts at high pressures and temperatures.¹

The direct transformation of C–H bonds of this primary feedstock to selective, high-valued C–X bonds is thus greatly desirable, and has found felicitous applications for X = C, N, O, S, B, and halogen atoms. However, C–N bond-construction protocols² to effect aminations of inert primary/secondary C(sp³)–H and aromatic C(sp²)–H bonds remain challenging. The importance of the C–N bond, as a functional element of chemicals pervading the modern industrial world (polymers, agrochemicals, pharmaceuticals, semiconductor and catalytic materials, solvents, household chemicals), cannot be underestimated. The gold standard for challenging amination protocols rests on the C–N cross-coupling reaction (Ullmann, Buchwald-Hartwig, Chan-Lam),³ which, however, requires pre-functionalization of the C–H bond to generate an energetic C–X derivative (X = halides, pseudohalides, boronic acids, stannanes, siloxanes), and frequently involves extensive heating. The desirable direct amination of C–H bonds by means of metal-nitrene, metal-nitrenoid or metal-amide entities, involving largely platinum-group elements, but also emerging nonprecious metals, has become a field of intense exploration (Scheme 1).^{4–9} Metal-free nitrenes, nitrenoids and aminyl/amidyl/imidyl radicals or even nitrenium ions can also be effective, albeit not always selective agents.^{10–15} The C–N bond construction technology requires further development to encompass substrates that extend beyond the current feedstock of rather weak or energetic C–H bonds (usually benzylic, tertiary, or heteroatom-activated C–H bonds) in order to employ raw starting materials from primary energy sources (natural gas, petroleum). Recent work has emphasized approaches that rely on substrate-appended directing groups to guide site-selective functionalization of inert C–H bonds.^{16–20} Although this methodology is certainly beneficial for C–H aminations related to the needs of selective synthesis of

pharmaceutical agents, it is rather inept for synthetic targets derived directly from non-functionalized energy-related feedstock (for instance, C₁-C₈ alkanes and aromatics).

To appreciate the challenges associated with the amination of two iconic substrates (methane, benzene), suffice it to say that the direct amination of methane and benzene by ammonia to afford methylamine²¹ and aniline,^{22,23} respectively, (Scheme 2) are both endergonic processes and require a hydrogen scavenger to render them thermodynamically feasible. In heterogeneous catalysis, a suitable metal oxide (for instance, “cataloreactant” NiO)²² can eliminate hydrogen as water. In homogeneous catalysis, an “oxidant” is needed to provide a similar thermodynamic driving force. Common oxidants employed are hypervalent iodine(III) reagents (ArI=NR), organic azides (RN₃), haloamines (RNNaX, X = halogen), and F⁺ reagents (R₂N-F), or the less explored *O/N*-substituted hydroxylamines (RO-NR'R''),²⁴ which can transfer the nitrogen moiety (NR, NR₂) to be inserted in the C-H bond via metal-nitrene/nitrenoid chemistry.²⁵⁻²⁷ For example, if ammonia is replaced by the parent hydroxylamine (HO-NH₂), the iconic reactions of Scheme 2 become highly exergonic (eqs. 1, 2) by virtue of the strong O-H bond generated.²⁸ However, instances of unactivated prim/sec sp³-C-H and aromatic C-H bond aminations have been scarce and require a more systematic effort to unravel their potential.

In this paper we collect several representative literature examples that highlight the efforts of the community in developing methodologies that mediate intermolecular aminations of challenging sp³- and sp²-C-H bonds. We limit our discussion to substrates that are linear or branched light alkanes (C₁-C₁₀) and simple benzenes. Therefore, aminations of commonly employed cycloalkanes, benzylic substrates, heteroatom-activated C-H bonds, or functionalized aromatics and polyaromatics (including cases of residue-directed C-H aminations) are not covered, with the exception of some rare examples. We concentrate on metal-dependent catalytic systems, but also include metal-free aminations performed by nitrogen-donor systems that are also frequently encountered in tandem with metal reagents. With respect to the nitrogen-group donor, we cover predominantly nitrene/nitrenoid-based systems, but also include well-defined examples of analogous amide/imide-dependent reactions, since the latter systems can give rise to tertiary amines via non-nitrene pathways (Scheme 1). The review first examines cases in which common nitrogen-group donors give rise to diffusively-free nitrogen-centered units responsible for amination of light alkanes and benzenes under thermal or photolytic conditions. These cases serve as precautionary examples of potentially unintended consequences in the use of common nitrogen-group sources. The bulk of the review then surveys seminal examples of metal-dependent and metal-free aminations of light alkanes and benzenes, with emphasis on reactivity/selectivity and mechanistic understanding. Other reviews² discuss some of the topics elaborated in this paper, albeit as part of a wider coverage of C-N bondconstruction methodologies.

2. Aminations via Intervention of Diffusively-free Nitrogen-Centered Species

As a precautionary note, any approach that engages redox-active metal sites should entertain the possibility that diffusively-free, rather than metal-bound, nitrogen-centered entities (usually radicals) may serve as the primary vehicle for substrate amination. Conversely, the operation of “metal-free” or organocatalytic systems should always guard against the unintentional presence of even minute amounts of metal ions, which may prove to be essential elements of the amination activity. Although *N*-centered radical-based approaches can be exceptionally well suited for aminations of challenging substrates (see below for examples), and may even require metal assistance for their generation, those should be distinguishable from systems that operate via bona fide metal-bound nitrogen donors, but such a distinction may not be easy to establish.

Organic azides (RN_3), for instance, are common partners of transition-metal reagents as nitrogen-group sources of amination reactions via metal-nitrene intermediates.²⁷ Yet, under thermal or photolytic conditions, the commonly used sulfonyl azides (RSO_2N_3 , R = alkyl or aryl) are known²⁹ to liberate ground-state singlet nitrenes that can insert into the C–H bonds of alkanes or add to aromatic rings. For example, 1-pentane-, 2-propane-, and *p*-toluene-sulfonylazides (Scheme 3(a)) react with cyclohexane at elevated temperatures to provide the corresponding cyclohexyl- $NHSO_2R$ products in good yields, accompanied by very little RSO_2NH_2 . Under the same thermal conditions, *p*-Tolyl SO_2N_3 reacts with 2-methylbutane (Scheme 3(b)) to provide all possible products of amination ($(3^\circ + 2^\circ)/1^\circ = 1.53$). The thermally or photolytically-generated carbethoxy nitrene from $EtOC(O)N_3$ aminates 2-methylbutane (Scheme 3(c)) more selectively ($3^\circ/2^\circ/1^\circ \approx 32:10:1$ (per H atom)).³⁰ Moreover, thermally-generated *p*-Tolyl SO_2N nitrene adds to benzene twice as fast as it inserts into the C–H bonds of cyclohexane, whereas addition to *p*-xylene is 2.2 times faster than that of benzene.²⁹ These results, along with comparative rates of $MeSO_2N$ addition to substituted benzenes (anisole > toluene > benzene > chlorobenzene 2.54: 1.86: 1: 0.44; Scheme 3(d)),³¹ are consistent with the highly electrophilic nature of the sulfonylimido active entities. Interestingly, the positional selectivity for $MeSO_2N$ attack on C_6H_5-X (X = MeO, Me, Cl; Scheme 3(d)) is highly favoring the *ortho* and *para* positions almost equivalently (very little *meta* products are observed), and cannot be fully rationalized by a typical homolytic (radical) aromatic substitution mechanism with an electrophilic radical. Rate-determining singlet-nitrene attack to form an aziridine intermediate is instead preferred (Scheme 3(e)), followed by selective product-determining C–N bond cleavage (heterolytic). In all processes noted above, any residual RSO_2NH_2 is presumed to be the product of H-atom abstraction from the substrate by the corresponding triplet nitrene.

As a further illustration of the power of metal-free nitrogen-centered intermediates, several redox-active ions (Fe^{II} , Cu^I , V^{III} , Ti^{III}) and solid-state (photo)catalysts are known^{22,32–34} to generate diffusively-free or surface-adsorbed neutral or protonated amino radicals ($\cdot NR_2$, $\cdot NHR_2^+$) from various sources (*N*-haloamines, *N/O*-substituted hydroxylamines, ammonia), which can in turn aminate aliphatic and aromatic substrates at high rates. For instance, Minisci has shown³⁵ that catalytic or stoichiometric amounts of metal salts (Fe^{II} ,

Ti^{III}, Cu^I, Cr^{II}) can activate *N*-alkylchloramines in acidic media to give rise to amino radical cations $\bullet\text{NHR}_2^+$ that can perform homolytic aromatic aminations (Scheme 4(a)).³⁶ Anisole undergoes facile amination by $\bullet\text{NHMe}_2^+$ exclusively at *ortho* and *para* positions (*o/p* 37: 63), whereas halobenzenes deactivate the benzene ring, but otherwise direct amination predominantly at *ortho/para* positions, not unlike the selectivity established for electrophilic aromatic substitutions ($\text{S}_{\text{E}}\text{Ar}$). In sharp contrast to the $\text{S}_{\text{E}}\text{Ar}$ paradigm, alkyl-substituted benzenes exhibit low positional selectivity, with significant *meta* substitution and steric sensitivity.³⁷ Benzylic amination is concurrent with aromatic activation, but occurs to a very low extent. Electron-poor benzenes are strongly deactivating, but introduction of an extra electron-donating substituent may counteract the effect. These trends have been rationalized^{35–37} by invoking strong polar contributions (Scheme 4(b)) in the addition of the highly electrophilic alkylamino radical cation ($\bullet\text{NHR}_2^+$) to the aromatic ring, highlighted by a transition state with dominant charge-transfer character.

Finally, *O*-substituted hydroxylamines are currently emerging as good NH_2 donors in conjunction with transition-metal reagents,^{4k} but caution is necessary as they can easily generate diffusively-free $\bullet\text{NH}_2$ and $\bullet\text{NH}_3^+$ radicals. For example, very low concentrations of Fe(II) ions (even less than 1 mol%) can activate hydroxylamine-*O*-sulfonic acid ($\text{H}_2\text{N}-\text{OSO}_3\text{H}$) in acidic media, to generate free $\bullet\text{NH}_3^+$ radicals (Scheme 4(c)).³² Those attack mono-substituted benzenes with reactivity expected for electrophilic radical attack, and position selectivity that is significantly less discriminating versus that observed for the aforementioned alkylamino radical cations. This is likely due to the higher reactivity of the unsubstituted $\bullet\text{NH}_3^+$ radical (higher exothermicities), which gives rise to early transition states with less polar-effect sensitivity, leading to lower selectivity.

3. Pertinent Examples of Amination of Light Alkanes

Mansuy's Mn/Fe-Porphyrin Systems

Mansuy's pioneering study⁷ⁿ on the amination of alkanes by Mn(III) and Fe(III) porphyrins includes a detailed analysis of heptane amination by $\text{PhI}=\text{NTs}$. Several metaloporphyrins were examined ($\text{M}(\text{TPP})\text{Cl}$, $\text{M}(\text{TPP})\text{OTf}$ ($\text{M} = \text{Mn}, \text{Fe}$; TPP = tetraphenylporphyrin); $\text{Mn}(\text{TMP})\text{OTf}$ (TMP = tetramesitylporphyrin); $\text{Mn}(\text{TMPP})\text{OTf}$ (TMPP = tetra-2,4,6-trimethoxyphenylporphyrin); $\text{M}(\text{TDCPP})\text{OTf}$ ($\text{M} = \text{Mn}, \text{Fe}$; TDCPP = tetra-2,6-dichlorophenylporphyrin). Scheme 5 summarizes the product profile, showing total yields (based on $\text{PhI}=\text{NTs}$) and relative proportion (%) of each regioisomer. The only other product is TsNH_2 , providing product balances close to 100%. The catalytic reaction employs heptane in large excess (20 equiv.) over $\text{PhI}=\text{NTs}$, 5 mol% of catalyst, molecular sieves, and is conducted in anhydrous CH_2Cl_2 at 20 °C under argon.

Close inspection of the product profile indicates that the overall yields are low (3 – 13%), with $\text{Mn}(\text{TDCPP})\text{OTf}$ providing the highest value. The product distribution favors 2-tosylaminoheptane in all cases, with the important exception of $\text{Mn}(\text{TMP})\text{OTf}$ that elevates 1-tosylaminoheptane as the lead product. In fact, the yield of the primary tosylamine is low with the parent TPP porphyrin, but increases drastically, at the expense of all other regioisomers, with increasing steric bulk of the *ortho* substituent of the *meso*-phenyl porphyrin group. In general, the sum of the 1- and 2-substituted tosylamines surpasses the

sum of 3- and 4-substituted congeners (ratio of (1+2)/(3+4) ranges from 1.7 (Mn(TPP)Cl) to 4 (Mn(TMP)OTf)), the ratio increasing with the steric encumbrance of the porphyrin. Interestingly, the 3- and 4-substituted products are present in almost equal amounts per catalytic system hence the 4-substituted isomer is statistically favored. No major differences between Mn and Fe porphyrins are observed, save for the fact that the Mn-based systems provide somewhat higher yields, while the Fe congeners exhibit slightly higher selectivity in favor of 1- and 2-substituted isomers as a sum.

Further insights with respect to the enhanced regioselectivity for the amination of the more sterically accessible 1- and 2- sites of heptane are gained via comparisons to the observed regioselectivity for the hydroxylation of heptane by Mn(Porph)/PhI=O systems.^{38,39} Indeed, the relative proportion of 1-, 2-, 3-, and 4-heptanol (2: 37: 40: 21) with the least sterically demanding Mn(TPP)(OAc) system provides only miniscule amounts of 1-heptanol, and statistically equivalent amounts of the 2-, 3-, and 4-heptanols according to the number of hydrogen atoms present at each site. In contrast, the equivalent Mn-TPP based amination systems noted above are significantly more selective with respect to the relative proportions of 2-tosylaminoheptane (52%, major product) and 1-tosylaminoheptane (13%). As the bulk of the porphyrin increases due to *ortho* substitution of the meso-aryl groups, 2-heptanol too becomes progressively the major product (max. 65% for Mn(TDCPP)Cl). However, the sum of the relative proportions of the 1- and 2-substituted product, and most importantly the ratio of the relative proportions of the 1- over 2-substituted product, always remain higher for amination vs. hydroxylation for equivalent catalysts. The greater regiospecificity of the amination reaction in favor of the more accessible positions 1 and 2, has been assigned to the size of the metal-bound NTs moiety versus that of the oxo ligand.

In terms of mechanistic scenarios for the amination reaction, the authors prefer a hydrogen-atom abstraction from the substrate by a putative $M^V=NTs \leftrightarrow M^{IV}-\cdot NTs$ unit, to generate an incipient alkyl radical ($R^\cdot$) and an amido $M^{IV}-NHTs$ moiety, followed by radical recombination of the resulting species ($M^{IV}-NHTs + R^\cdot \rightarrow M^{III} + R-NHTs$). The proposed mechanism largely mirrors analogous concepts on the operational mode of well-explored metalloporphyrin/PhI=O systems,⁴⁰ and further takes into account the existence of metalloporphyrin-nitrene complexes at the time of the study.⁴¹⁻⁴³ In a single experiment, the catalytic reaction of cyclohexane with PhI=NTs, mediated by Mn(TDCPP)OTf, is shown to form chlorocyclohexane along with tosylaminocyclohexane and $TsNH_2$, suggesting that diffusively-free alkyl radicals may be viable intermediates.

He's Disilver(I) System

With a significant time lapse, the search for suitable catalysts for the amination of light alkanes was resumed by several groups, starting with an influential contribution by He's group.⁵¹ Capitalizing on previous studies involving the employment of coinage metals along with terpyridine^{44,45} ligands in the amidation of substrates, He's group makes use of a system (Scheme 6) composed of AgOTf (4 mol %) and 4,7-diphenyl-1,10-phenanthroline (bathophenanthroline, BP) (4.8 mol %) for the amination of 2-methylpentane (5 equiv.) by PhI=NNs in the presence of 4 Å molecular sieves. The catalyst AgOTf/BP is added in two equal portions (at the start of the reaction, and after two hours) in CH_2Cl_2 , and the reaction

is allowed to run overnight at 50 °C under nitrogen. The amination occurs exclusively at the tertiary position with a 22% isolated yield.

The authors have crystallized the complex formed by AgOTf and BP in CH₂Cl₂, and a single-crystal X-ray diffraction analysis has revealed that an intriguing disilver(I) compound is assembled, composed of two nonequivalent monomers. One silver(I) site is coordinated by BP and two triflate moieties (OTf), featuring a distorted square-planar geometry. The second silver(I) site is three-coordinate, encompassing a BP ligand and a water molecule (of unknown provenance) in a distorted trigonal geometry. The two units hold together presumably via aromatic BP⋯BP stacking interactions, and potentially an argentophilic⁴⁶ Ag(I)⋯Ag(I) contact (3.386(1) Å). There is no indication whether the disilver(I) assembly is retained in solution. Nevertheless, the authors consider the dimeric structure to be crucial to the catalytic operation, since 2- or 2,9-substituted (Me, *t*-Bu, Mesityl) phenanthrolines are detrimental to catalysis, apparently due to disruption of the dimeric structure.

Pérez's Silver(I)-Scorpionate Systems

A systematic study^{5f} of metal-scorpionate catalysts by Pérez and co-workers has provided the most effective systems for light alkane amination. Early indications of the advantages of coinage-metal complexes with scorpionate ligands has been furnished by studies of [Tp^{Br3}Cu(NCMe)] (Tp^{Br3} = hydrotris(3,4,5-tribromo)pyrazolylborate) as catalyst for the amination of cycloalkanes, aromatics, and alkylaromatics by PhI=NTs.^{5e} Notably, whereas alkylaromatics are preferentially aminated at the benzylic position, the β- position of the alkyl branch is also aminated to a smaller extent. Further inspiration was derived from ancillary studies that showed an improvement of catalytic activity in carbene C–H insertions upon replacement of copper(I) by silver(I).^{47,48} These initial observations, along with the preceding seminal contribution by He,^{5l} provided the impetus for examining four silver(I) scorpionate catalysts, namely, Tp*Ag, Tp^{*,Br}Ag, Tp^{Ms}Ag and Tp^{Br3}Ag (Scheme 7). It is noteworthy that these compounds are dinuclear ([Tp*Ag]₂, [Tp^{*,Br}Ag]₂, [Tp^{Br3}Ag]₂) or even trinuclear ([Tp^{Ms}Ag]₃[NO₃]) in the solid state, but are known to dissociate in solution to release a certain degree of the monomeric unit.

The amination (PhI=NTs) of four light alkanes (pentane, hexane, 2-methylbutane, 2,3-dimethylbutane), used in neat condition (5.0 mL), is conducted in the presence of 5 mol% catalyst at 80 °C for 4 hours (Scheme 7). The order of catalyst efficiency in terms of overall yield is Tp^{*,Br}Ag > Tp*Ag ≈ Tp^{Ms}Ag > Tp^{Br3}Ag for pentane and hexane, and Tp^{*,Br}Ag > Tp*Ag > Tp^{Ms}Ag > Tp^{Br3}Ag for the branched alkanes. The trend seems to favor electron-withdrawing substituents of the pyrazolyl backbone (Tp^{*,Br}Ag vs. Tp*Ag), potentially associated with enhancement of the electrophilic character of a putative metal-nitrene active species. Excessive congestion of the active site (Tp^{Ms}Ag, Tp^{Br3}Ag) is apparently detrimental to catalytic turnover, especially for the branched alkanes. For the linear alkanes, the primary position is aminated by all catalysts, save for Tp^{Br3}Ag, to a low extent (relative proportion: 5 – 15%), the highest activity being observed for Tp^{Ms}Ag, presumably due to the steric encumbrance effected by the bulky mesityl group to the more hindered secondary positions of the substrate. As expected, amination at position 2 provides the highest yielding product, although the regioselectivities for amination at positions 2 and 3 are not far from

statistical. For the branched alkanes, amination of the tertiary position is decidedly favored over secondary and primary positions. Only the secondary position of 2,3-dimethylbutane provides low yields of amination product, whose relative proportion versus tertiary amination is significantly enhanced with the more sterically hindered $\text{Tp}^{\text{Ms}}\text{Ag}$ and $\text{Tp}^{\text{Br}^3}\text{Ag}$ catalysts.

Mechanistic insights have been provided by a series of experiments involving the radical inhibitor 2,6-di-*tert*-butylhydroxytoluene (BHT). Addition of 10 equiv. of BHT over catalyst ($\text{Tp}^{\text{Br}}\text{Ag}$) to the catalytic reaction of hexane with $\text{PhI}=\text{NTs}$, reduces the overall yield from 70% to 10%, while the relative proportion of regioisomers remains largely the same. Addition of 2 equiv. of BHT to the catalytic reaction of 2,3-dimethylbutane with $\text{PhI}=\text{NTs}$, mediated by each of the four silver catalysts noted above, curtails all products by approximately 50%. A series of analogous catalytic experiments, apparently mediated by the leading catalyst $\text{Tp}^{\text{Br}}\text{Ag}$, involving variable molar ratios of BHT/ $\text{PhI}=\text{NTs}$ ranging from 0 to 1.0, indicate progressive inhibition of the amination of 2,3-dimethylbutane (from 75 to 0%). It is not clear whether a plateau region may be present, which can assist in distinguishing between solvent-caged and diffusively-free capturing of radicals.⁴⁹ These experiments, as well as others involving amination of cycloalkanes and aziridination of alkenes by the silver(I) reagents, are consistent with a global mechanistic scheme that employs a biradical silver-nitrene unit ($^3[\text{Ag}^{\text{II}}-\text{NTs}]$) performing hydrogen-atom abstraction from alkanes ($\text{R}-\text{H}$), followed by radical rebound of the resulting substrate radical ($\text{R}\cdot$) and the $\text{Ag}^{\text{II}}-\text{NHTs}$ amido species, in a manner analogous to that detailed in the case of metalloporphyrin-nitrene species.

Dirhodium(II) Carboxylate vs. Silver(I) Scorpionate Systems

A seminal study^{4d} by Müller, Dodd, and Dauban on the stereoselective C–H amination of hydrocarbons by a suite of chiral dirhodium (II) carboxylate reagents (paddlewheel structures), identified $\text{Rh}_2(\text{S-nta})_4$ ($\text{nta} = N$ -(1,8-naphthoyl)-alanine) as a promising catalyst for the amination of a host of substrates (benzylic, allylic, unfunctionalized alkanes) with chiral sulfonimidamides, providing excellent yields and diastereoselectivities. The only light alkane examined, 2-methylbutane (5 equiv.), is aminated by (*S*)-*N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidamide in the presence of $\text{Rh}_2(\text{S-nta})_4$ (5 mol%), oxidant $\text{PhI}(\text{OCO}t\text{-Bu})_2$ (1.4 equiv.), and 4 Å molecular sieves, in $\text{Cl}_2\text{CHCHCl}_2/\text{MeOH}$ (3:1) at -35°C for 3 days under argon (Scheme 8, noted as *c*). The amination occurs exclusively at the tertiary position with a 36% isolated yield. The authors favor an asynchronous concerted metal-bound nitrene insertion into the C–H bond, but cannot exclude an H-atom abstraction/radical rebound mechanism.

This initial exploration prompted a more detailed, comparative study⁵⁰ of catalytic C–H amination of alkanes, mediated by the leading reagents $\text{Rh}_2(\text{S-nta})_4$ and $\text{Tp}^{\text{Br}}\text{Ag}$ (Scheme 8). The aforementioned chiral sulfonimidamide (1.0 equiv.) is employed with both catalysts, coupled with the oxidant $\text{PhI}(\text{OAc})_2$ (1.2 equiv.). Initially, the amination of pentane by $\text{Tp}^{\text{Br}}\text{Ag}$ (4 mol%) suggested that the reaction can be optimally conducted with only 5 equiv. of pentane (rather than in neat alkane) in CH_2Cl_2 at 40°C , to afford 70% yield of combined product, with a regioselectivity of 24: 47: 29 (1-, 2-, 3-amine) and poor

diastereoselectivity (55/45) for the 2-amine. The corresponding reaction with $\text{Rh}_2(\text{S-nta})_4$ (3 mol%) in $\text{Cl}_2\text{CHCHCl}_2/\text{MeOH}$ (3:1) at -35°C over 4 Å molecular sieves under argon, only provides 14% yield over 72 hours. These conditions are further explored with a suite of branched $\text{C}_5\text{--C}_8$ alkanes (Scheme 8), to reveal that the tertiary position is exclusively aminated, and that $\text{Tp}^{*,\text{Br}}\text{Ag}$ is a more efficient catalyst than $\text{Rh}_2(\text{S-nta})_4$ for all substrates, with the exception of 2-methylbutane. Moreover, increasing the amount of substrate drastically improves the yield for the silver(I) but not the dirhodium(II) reagent. The latter system also gives no product at room temperature.

Che's Ruthenium(IV) Porphyrin System

In a single entry, Che reports^{6c} the amination of hexane (20 equiv.) by the phosphoryl azide $(\text{CCl}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{N}_3$ in the presence of $[\text{Ru}^{\text{IV}}(\text{F}_{20}\text{-TPP})\text{Cl}_2]$ (2 mol %) and 4 Å molecular sieves, conducted in refluxing 1,2-dichloroethane (84°C) under argon for 12 hours (Scheme 9). A combined 76% yield is reported for the two amination products obtained (positions 2 and 3) with a largely statistical distribution (2.3: 1). In contrast, 2,3-dimethylbutane provides trace quantities of product, presumably due to steric inaccessibility of the electronically favored tertiary position. Based on a sizeable kinetic isotope effect value ($k_{\text{H}}/k_{\text{D}} = 5.1$), albeit for the cyclohexane/cyclohexane- d_{12} amination by the phosphoryl azide, the authors favor a hydrogen-atom abstraction/radical rebound mechanism for this system.

Miscellaneous Metal-centered Nitrene-based Systems

In a single example, Stavropoulos and co-workers⁵¹ show (Scheme 10) that the light alkane 2-methylbutane (limiting reagent) can be aminated by PhINTs (2.0 equiv.) in the presence of $[\text{Cu}^{\text{I}}(\text{TMG}_3\text{trphen})][\text{PF}_6]$ (10 mol%) and 5 Å molecular sieves in MeCN/chlorobenzene (1:10 v/v) at room temperature. The tertiary position is exclusively aminated in moderate yields (36%). Interestingly, if the reaction is conducted in acetonitrile, products of amidination (major) and aziridination (minor) are obtained along with trace amounts of the amination product. This reactivity pattern highlights the intervention of substrate-centered *tert*-carbocations, most likely generated via oxidation of diffusively-free carboradicals by Cu(II), which is facile for tertiary positions. Ritter-type addition^{52,53} of the carbocation to MeCN at the N-atom terminus provides the amidination product, while E1-type proton elimination from the carbocation affords olefins, which proceed to undergo aziridination. DFT calculations suggest that an elusive triplet copper-nitrene $^3[\text{Cu}^{\text{II}}\text{--}^*\text{NTs}]$ may be the H-atom abstracting entity, featuring a $k^1\text{-N}$ (NTs) coordination mode and an elongated equatorial Cu–N residue (2.93 Å). Proposed mechanistic steps associated with the action of the copper-nitrene species are illustrated in Scheme 11 and involve both solvent-caged and out-of-cage events.

Notably, Nicholas and Houk^{5c} favor a $k^2\text{-N,O}$ (NTs) bidentate mode for a putative cationic bis(imine) copper-nitrene intermediate with a triplet ground state. The same $k^2\text{-N,O}$ (NTs) coordination mode has been assigned by Ray⁵⁴ to an isolable copper-nitrene species supported by a tridentate amine ligand, and further stabilized by a Lewis acid, as for instance in $[(\text{LCu}^{\text{II}}\text{--}^*\text{NTs})\text{Sc}(\text{OTf})_3]^+$,^{54a} although the coordination site of the cation is uncertain.^{54b} In this case, as well as in the case of an isolable Cu–NMes monodentate congener,^{54c} the ground state is experimentally and computationally deduced to be an open-shell singlet,

narrowly separated by a triplet excited state. Warren and co-workers^{5a, 5b, 55} have noted several instances of reactive Cu=NR entities (R = aryl, 1-adamantyl, *tert*-butyl, cyclohexyl, -CH₂CH₂Ph) in equilibrium with isolable bridging dicopper nitrenes, [Cu]₂(μ-NR), supported by β-diketiminato ligands. Finally, Bertrand and Frenking⁵⁶ have characterized several Cu and Ag triflate complexes bound by nucleophilic phosphononitrenes, with variable stoichiometries ([(TfO)M]₂(μ-NR), [(TfO)M(NR)], [M(NR)₂](OTf); M = Cu, Ag). However, all these metal-nitrene species have been shown to aminate, at most, cycloalkanes, alkylaromatics and other energetic C–H bonds, and as such are not further reviewed here.

Ochiai's Metal-free Alkane Amination System

Spectacular aminations of light alkanes have been reported by Ochiai⁵⁷ with the hypervalent Br(III) sulfonylimino-λ₃-bromane 4-CF₃C₆H₄-Br^{(+)-(−)}NSO₂CF₃ (Scheme 12). As opposed to imino-λ₃-iodanes, which require metal activation, the bromane reagent can perform metal-free aminations of a series of alkanes, provided in excess either in neat condition or in the presence of 20 equivalents of hexafluoroisopropanol (HFIP) at room temperature under argon for 10 to 24 hours. The reactions in the presence of HFIP provide significantly better yields and indicate a selectivity pattern that favors amination of 3° over 2° C–H sites, while no primary C–H activation is observed. Secondary sites (as in hexane) are aminated with comparable selectivity, whereas the bulky 2,2,4,4-tetramethylpentane is recovered intact.

Kinetic studies reveal that the rates of amination of alkanes by the imino-λ₃-bromane obey second-order kinetics with negative activation entropies, whereas the relative rate of activation per C–H site correlates with the C–H bond dissociation energy. These results, along with retention of stereochemistry and modest KIE values observed with diagnostic cycloalkanes, are best accommodated by a mechanism that involves a concerted asynchronous (N–H first) insertion of the Br-bound nitrene (NTf) into the C–H bond. DFT studies conducted with ethane, propane and isobutane are in agreement with this mechanistic scenario and further support an early transition state for the 3° vs. the 2° C–H bond activation, as reflected in the lower KIE values for the amination of the *tert*-C–H bonds of adamantane ($k_H/k_D = 1.49$) versus the *sec*-C–H sites of cyclohexane ($k_H/k_D = 3.72$).

Copper Non-Nitrene Mediated Amidation and Imidation Systems (Hartwig, Kanai)

Two closely related studies by Hartwig⁵⁸ and Kanai⁵⁹ examine copper-catalyzed reactions of light alkanes (among other substrates) with various primary and secondary amides, carbamates, phthalimides, and isocyanates, using di-*tert*-butyl peroxide as oxidant. In contrast to the cases noted above, in which a putative metal-nitrene species is considered responsible for H-atom abstraction, the Hartwig and Kanai systems engage *tert*-butoxy radicals as the primary H-atom abstraction entities. Preceding studies by Warren and co-workers^{60, 61} have provided similar ^tBuOO^tBu-based protocols, involving amination of alkylaromatics and cycloalkanes (but not light alkanes or benzenes) by a host of primary and secondary alkyl and aryl amines.

Hartwig's study⁵⁸ explores the benzamidation of two light alkanes, 3-ethylpentane and 2,4-dimethylpentane, used in excess (1.0 mL), in the presence of ^tBuOO^tBu (4.0 equiv.) (Scheme 13(a)). The copper catalyst is assembled in situ by adding CuI (2.5%) and 4,7-

(MeO)₂-1,10-phenanthroline (2.5 %) to the catalytic mixture in *o*-C₆H₄Cl₂, and the reaction is allowed to run for 36 hours at 100 °C. Remarkably, the benzamidation of 3-ethylpentane occurs only at the secondary and primary positions in a 2:1 ratio, whereas that for 2,4-dimethylpentane functionalizes the primary position exclusively.

By means of a multitude of diagnostic experiments and insightful kinetic analysis, largely employing cyclohexane, phthalimide (or benzamide), and *t*BuOO*t*Bu, along with well-characterized (phen)Cu^I-phth and (phen)Cu^{II}-(phth)₂ compounds (phth = deprotonated phthalimide), the authors suggest mechanistic steps (Scheme 13(b), adapted for PhCONH₂) that operate via turnover-limiting H-atom abstraction from the substrate by *t*-BuO• radicals, generated via Cu(I)-assisted decomposition of *t*BuOO*t*Bu (eq. 1). The intriguing regioselectivity observed can be attributed to steric hindrance, especially if the substrate-centered radical recombines with the metal center (eq. 3) prior to undergoing reductive elimination with the amide (or imide).

Kanai's study⁵⁹ examines the carbamation of hexane (10 equiv.) by phenyl isocyanate, in the presence of *t*BuOO*t*Bu (2.5 equiv.) as oxidant, mediated by a copper catalyst assembled from [Cu(NCMe)₄][BF₄] (5 mol%) and 2,9-dimethyl-1,10-phenanthroline (5 mol%), operating in trifluorotoluene at 100 °C over 24 hours (Scheme 14). All sites undergo carbamation in 56% overall yield, with regioselectivity (1: 3.2: 1.4 (1-/2-/3-)) favoring position 2. Unfortunately, the carbamation of any branched light alkane is not reported. Interestingly, isocyanates (R–N=C=O) provide significantly higher yields than the corresponding secondary carbamates (R–NC(O)O*t*Bu), although the former affords the latter in the presence of *t*BuOO*t*Bu. Mechanistic analysis provides an operational manifold that is largely the same as that proposed by Hartwig, save for the fact that the potential role of Cu(I) in the generation of *t*-BuO• from *t*BuOO*t*Bu is not recognized.

4. Pertinent Examples of Catalytic Amination of Benzenes

Sadighi's Cu(I) Phenanthroline Systems

Sadighi's intriguing contribution⁶² (Scheme 15) is among the earliest reports of putative metallo-nitrene insertion into aromatic C–H bonds. Two Cu(I) compounds with 2,9-bis(pentafluorophenyl)-1,10-phenanthroline (L¹) and 2,9-bis-[2',4',6'-tris(trifluoromethyl)phenyl]-1,10-phenanthroline (L²) ligands are synthesized and shown to obey different stoichiometries, namely, [Cu(L¹)₂][SbF₆] and [Cu(L²)][SbF₆], respectively. The latter complex, featuring the more bulky ligand, is electronically and coordinatively unsaturated, although it could form an η^2 -benzene adduct.

This compound, in only 0.5 mol%, can mediate the reaction of anisole (17 equiv.) and PhI=NTs in the presence of 3 Å molecular sieves in trifluoromethane, under ambient temperature and inert atmosphere, to afford *ortho* and *para* sulfonamidation products. Unfortunately, yields are not provided, although the presence of TsNH₂ and intractable oligomers are noted. More details are furnished for the electron-rich substrate 1,3-dimethoxybenzene (20 equiv.), which can undergo amination by PhI=NTs, mediated by [Cu(L²)][SbF₆] (1.8 mol%), under the aforementioned conditions, affording the product of *para* sulfonamidation in 63% yield. Notably, when the substrate is used in limiting amounts

versus PhI=NTs (1.4 equiv.), the product of double rather than mono sulfonamidation is formed in 33% yield. Other products include undefined sulfonated oligoarylamines. It is unclear whether products of activation of the methoxy group are present. Mechanistic insights are not offered, although an unstable green product arising from the interaction of Cu(I) and PhI=NTs is noted.

Pérez's Copper(I)-Scorpionate Systems

In what seems to be the earliest report of aromatic amination via metallonitrene chemistry, Pérez and co-workers⁶³ provide details on the operation of a copper-homoscorpionate compound, $\text{Tp}^{\text{Br}_3}\text{Cu}(\text{NCMe})$, which is capable of mediating (in 5 mol%) the amination of neat benzene (10 mL) by PhI=NTs , in the presence of molecular sieves, under ambient temperature and inert atmosphere over 12–18 hours (Scheme 16(a)). The resulting sulfonamidated benzene is obtained in 40% yield, while TsNH_2 (60%) accounts for the remaining mass balance. Alkylaromatics are aminated exclusively at the alkyl branch.

In a subsequent, more detailed account,^{5e} Pérez discloses that the yield of benzene amination by PhI=NTs can be doubled (80%) if the reaction is conducted at 85 °C. Moreover, under the conditions noted above, and at elevated temperature (80 °C), even an electron-deficient benzene, such as chlorobenzene, can undergo amination by PhI=NTs in 38% overall yield, split almost statistically between the *ortho* (26%) and the *para* (12%) aminated product, along with TsNH_2 (62%). In contrast, trifluorotoluene is inert, and anisole shows signs of MeO activation. Interestingly, under the same conditions, pyridine is aminated at the *ortho* position (35%), as well as the N atom to yield the $\text{C}_6\text{H}_5\text{N-NTs}$ zwitterion as the major product (65%).

A computational analysis (DFT) of the mechanistic intricacies of the $\text{Tp}^{\text{Br}_3}\text{Cu}(\text{NCMe})$ -mediated amination of benzene by PhI=NTs has been reported by Bao and co-workers.⁶⁴ The authors discuss optimized structures, at various level of theory (with emphasis on the M06 functional), for the triplet, singlet, and open-shell singlet Cu–NTs species in two geometrical forms ($k^2\text{-N,O}$ and $k^1\text{-N}$ nitrene-binding modes), concluding that the triplet configuration is the ground state for both coordination isomers, separated by at least 10 kcal mol^{−1} from the singlet and open-shell singlet states.⁶⁵ Furthermore, the two unpaired electrons of the triplet state are heavily localized on the N atom. Importantly, the $k^2\text{-N,O}$ -containing structure lies energetically lower than the $k^1\text{-N}$ congener by approximately 2 kcal mol^{−1}. The reaction trajectory of the $^3[\text{Cu-NTs}]$ unit ($k^2\text{-N,O}$ binding mode) versus benzene (Scheme 16(b)) is then computed to favor addition of the metallo-nitrene moiety to benzene (as opposed to H-atom abstraction), followed by formation of a singlet metallo-aziridine type intermediate via spin crossover. The loss of aromaticity is subsequently restored by cleavage of one the C–N bonds, followed by 1,2-H atom shift from C to N. Alternatively, the product can be reached directly from the triplet metallo-nitrene benzene adduct via 1,2-H atom shift, but this aziridine-bypassing path seems to be more energetically demanding. The study does not consider potential paths involving one-electron oxidation of the cyclohexadienyl radical intermediate, followed by loss of a proton, which may be facilitated by internal aryl-to-metal electron transfer.

Gold(III)-Mediated Systems (He, Zhang)

In an influential communication,⁶⁶ He explores the amination of several substituted benzenes (8 equiv.) by PhI=NNs in CH_2Cl_2 at room temperature, catalyzed by AuCl_3 (2 mol %). Whereas benzene itself and mono- or di-substituted benzenes afford product in less than 5% yield, higher substituted benzenes provide impressive instances of aromatic amination (Scheme 17). Thus, mesitylene is aminated exclusively at the aromatic ring in high yields (90%), whereas 1,3,5-triethylbenzene is aromatically aminated (in 70% yield) with less than 5% amination at the benzylic position. Significant benzylic amination is only observed in the presence of tertiary alkyl substituents, as for instance in the case of 1,3,5-triisopropylbenzene, which exhibits aromatic vs. benzylic amination in a ratio of 1: 1.5. Interestingly, aromatic amination of 1,2,4-trimethylbenzene occurs at all three available aromatic positions in equal amounts.

The authors propose a mechanistic scheme that relies on electrophilic metallation (auration) of the aromatic ring (and aliphatic branch), based on a KIE value of 1 for the competitive amination of mesitylene and mesitylene- d_{12} (excluding a rate-determining C–H bond activation step), and more importantly due to observed deuteration of the metallated aromatic and benzylic positions of 1,3,5-triisopropylbenzene by D_2O in the absence of PhI=NNs (Scheme 17, bottom). It is less clear, however, how the nitrene source is activated and inserted into the aromatic and benzylic C–H bonds.

More recently, Bao and Schaefer⁶⁷ have provided computational analysis (DFT) to address some of the questions surrounding the Au(III)-catalyzed insertion of nitrene (NNs) into the aromatic C–H bond of mesitylene in He's study.⁶⁶ Scheme 18 summarizes essential steps that are considered as most favorable among many other alternative pathways. Most intriguing of the proposed intermediates are an initially generated gold(III) nitrenoid (Au-NNs(Cl)), as opposed to a thermodynamically unfavorable Au(III)-nitrene, and a subsequently formed Au(III)–mesityl species by virtue of a σ -bond metathesis that intrinsically preserves the aromaticity. The formation of the arylgold intermediate is not turnover-limiting (hence no significant KIE value is observed), since it is associated with a lower energy barrier than that calculated for the generation of the gold nitrenoid and the downstream formation of the C–N bond via reductive elimination, both estimated at approximately 29 kcal/mol. The preponderance of aromatic over benzylic C–H bond activation is assigned to a higher energy barrier for the cleavage of the C–H bond due to loss of aromaticity in the latter case.

In a related, more recent study, Zhang and co-workers⁶⁸ examine the amination of aromatics with azodicarboxylates ($\text{RCO}_2\text{-N=N-CO}_2\text{R}$; $\text{R} = i\text{-Pr, CCl}_3\text{CH}_2$), mediated by AuCl_3 (1 – 5%) (Scheme 19). In accordance with He's study,⁶⁶ benzenes (2 equiv.) with three or more electron-donating substituents can be aminated by $\text{PrCO}_2\text{-N=N-CO}_2\text{Pr}$ in the presence of AuCl_3 (1 mol%) in dichloromethane at room temperature (10 min – 24 h) in good to excellent yields (66 – 98%). In some cases (mesitylene), the bisaminated product is also obtained. More importantly, less electron-rich benzenes can be aminated, provided that the more electron-deficient $\text{CCl}_3\text{CH}_2\text{CO}_2\text{-N=N-CO}_2\text{CH}_2\text{CCl}_3$ is used instead, along with 5 mol % of AuCl_3 in dichloromethane under room temperature (1 – 2 days). In fact, benzene provides exclusively the 1,4-bisaminated product, whereas toluene affords both mono (*para*/

meta = 7:3) and bis-substituted (*m,m/p,p* = 1:1) products. Halobenzenes are aminated exclusively at the *para* position. Limited mechanistic analysis indicates that AuCl₃ interacts with azodicarboxylates only in the presence of arenes, and that the competitive bromobenzene/bromobenzene-*d*₅ amination affords a KIE value of 1. The authors put forth a mechanistic scenario (Scheme 20) that is similar to that proposed by He (auration, followed by azodicarboxylate activation). However, the fact that the amination of challenging benzenes is accessible with more electron-deficient azodicarboxylates generates some concerns about the actual role of AuCl₃. This is particularly true for CCl₃CH₂CO₂-N=N-CO₂CH₂CCl₃, which has been known⁶⁹ to effect *para*-directed amination of several electron-rich benzenes in the presence of various Lewis acids (LiClO₄/ether (3M), ZnI₂ or ZnCl₂ in CH₂Cl₂, CF₃SO₃H in CH₂Cl₂, neat CCl₃CO₂H).

Jensen's Fe(II)-Scorpionate Systems

In a most intriguing study,⁷⁰ Jensen investigates a series of first-row transition-metal reagents coordinated by either 3,5-disubstituted tris(3,5-R¹,R²-pyrazol-1-yl)methane or hydrotris(3,5-R¹,R²-pyrazol-1-yl)borate, with a general stoichiometry of [(L)M^{II}(NCMe)₃](BF₄)_{*n*} (*n* = 2 or 1, M = Mn, Fe, Co, Ni). Screening of these catalysts in styrene aziridination and THF α-C-H amination by PhI=NTs, provides evidence for the superior efficiency of the iron(II) reagent [(L)Fe^{II}(NCMe)₃](BF₄)₂ (L = tris(3,5-Me₂-pyrazol-1-yl)methane).

When this Fe(II) catalyst (in 5 mol%) is applied to the amination of a suite of benzenes (20–33 vol.% in CH₂Cl₂) by PhI=NTs at 20 °C (Scheme 21), aromatic amination is obtained in good yields (45 – 81%). As opposed to the AuCl₃-catalyzed aromatic aminations,^{66–68} the present Fe(II) system mediates aromatic amination of benzene, as well as of mono- and di-substituted benzenes. Remarkably, this system favors aromatic amination over benzylic amination, in sharp contrast to Pérez's copper-scorpionate catalyst.^{5e} Yields for aromatic amination increase with increasing electron-rich character of the aromatic substrate, whereas the relative proportion of benzylic amination increases in the order *prim* < *sec* < *tert* with respect to the alkyl branch. The regioselectivity of the aromatic amination favors exclusively the *para* (major) and *ortho* sites, with relative proportions for amination at the *ortho* position decreasing with increasing substituent size. Whereas these results point towards the intervention of an electrophilic Fe=NTs moiety, detailed mechanistic studies are not currently available.

Nicholas' Cu(I)-Phenanthroline System

Amidation of an impressive series of electron-rich and electron-deficient benzenes (employed neat, 1.0 mL) by *N*-tosyloxytrichloroethylcarbamate has been achieved by Nicholas and co-workers,⁷¹ with the assistance of a catalyst composed of [Cu(NCMe)₄]PF₆ (20 mol%) and 2,9-dimethyl-1,10-phenanthroline (neocuproine) (20 mol %), operating at 140 °C (sealed tube) for 8 hours (Scheme 22). The catalytic system is selected by screening several Cu(I) and Cu(II) complexes with different ligand systems. Under the conditions noted above (albeit over 16 hours), benzene provides the *N*-phenyl carbamate product in 75% yield. A series of mono-substituted benzene with electron-donating substituents (Me, Et, *t*-Bu, MeO) provide all *ortho/meta/para* carbamate products in moderate to good yields (36 – 59%). The presence of *meta* products contrasts sharply to the exclusive *ortho/para*

regioselectivity recorded in the studies of Pérez^{5e} and Jensen.⁷⁰ The low end of the product yield range is observed for *t*-Bu substituted products, probably due to the absence of the *ortho* product owing to hindrance. Amination at benzylic positions is not observed, although some undefined alkyl-arene coupling dimers are detected in the amination of toluene.

Importantly, benzenes with electron-withdrawing substituents (Cl, CF₃) are also aminated. In particular, chlorobenzene provides the highest yield (63%) obtained in this study, and an almost equimolar ratio of *ortho/meta/para* products. In addition, it reacts at faster rates than benzene by a factor of 8.8, as indicated in a competitive study. In comparison, anisole and toluene are aminated faster than benzene by a factor of 7.2 and 3.2, respectively, while *tert*-butylbenzene is aminated at slower rates with respect to benzene. These competitive data do not provide any linear Hammett correlations with respect to polar and/or spin-delocalization (radical) parameters, and may be better accommodated by more than one mechanistic scheme depending on substitution (one-electron vs. two-electron aromatic addition of a putative electrophilic copper-nitrene).

Hypervalent Iodine(III) Mediated Systems

(a) Metal-free Imidations (Cho-Chang, DeBoef, Antonchick, Muñiz)—Of great interest are metal-free approaches to aromatic aminations, especially those relying on hypervalent I(III) oxidants (usually PhI(O₂CR₃)₂; R = H, F) to simultaneously activate N-H and C-H (arene) bonds, leading to C-N coupling. These methods are largely limited to cyclic imides, and require high reaction temperatures. In a leading contribution,¹³ Cho and Chang reveal that benzene (either neat, or using 3 equiv. in 1,2-dichloroethane) can be imidated in 56 – 99% yield by a wide range of cyclic imides (succinimide, glutarimide, phthalimide derivatives, 1,8-naphthalimide, saccharin), in the presence of PhI(OAc)₂ (5 equiv.) as oxidant, at 140 °C over 4 hours. Phthalimide itself is among the best yielding imido sources, and can effect imidation of a series of arenes (Scheme 23) under the conditions noted above, but with less oxidant (3 equiv.). Good to high yields of phthalimide are obtained, although regioselectivities are unremarkable (all *o/m/p* products are observed). Moreover, specifically for sulfonimides (saccharin, as well as the acyclic (PhSO₂)₂NH), benzylic imidation occurs at the expense of aromatic imidation at 120 °C. Limited mechanistic data suggest that the oxidative arene imidation, which shows no kinetic isotope effect and is significantly faster for electron-rich arenes, obeys a typical electrophilic aromatic substitution path, involving preformed [PhthN-I(OAc)Ph] or [PhthN=I-Ph]⁺ species, both detected by ESI-MS. However, the poor regioselectivity cannot be easily accommodated by this S_EAr mechanism alone. Benzylic imidation, which exhibits a significant KIE (2.6 for toluene) and is kinetically independent of sulfonimide concentrations, is assigned to initial substrate oxidation to the benzylic carbocation by PhI(OAc)₂, followed by nucleophilic attack of the sulfonimide.

Almost contemporaneously with the Cho-Chang contribution, DeBoef and co-workers⁷² disclosed an almost identical system for the imidation of aromatics by several cyclic imides, although only phthalimide and succinimide provide good yields (Scheme 24). Notably, the substrate can be present as solvent (4.0 mL), but also in small excess (1.5 equiv.) over the imide along with MeCN (4.0 mL). The oxidant (PhI(OAc)₂) is limited from 1.5 to ideally

2.5 equiv., and the reaction operates at 145 °C under microwave heating. Regioselectivities do not differ much versus those reported by Cho-Chang,¹³ and appear to be directed by electronic parameters to a certain extent.

Neither C–H (arene) nor N–H (cyclic imide) bond activation is considered to engage in the turnover-limiting step, since KIE values for intermolecular C–H/C–D (benzene-*d*₆) and N–H/N–D (phthalimide-*d*) competition are close to 1. Importantly, kinetic analysis establishes a first-order relationship with respect to phthalimide and oxidant. Although a S_EAr mechanism is consistent with this result, the observed regioselectivity is not in line with a bona fide electrophilic aromatic substitution. For instance, imidation of toluene provides a mixture of *o*/*m*/*p* products in a ratio of 10:6:5, and furthermore *ipso* substitution is observed with *p*-R-anisoles (R = Me, ^tBu). Unfortunately, toluene is the only mono-substituted aromatic employed. The authors opt for a single-electron transfer mechanism (Scheme 25), which generates an arene radical cation intermediate (but also an uncertain I(II) species), followed by nucleophilic attack by the imine. The formation of arene radical cations by the stronger I(III) hypervalent oxidant PhI(O₂CCF₃)₂ has been previously detected by UV and EPR spectroscopies.⁷³ The arene radical cation resonance structures provide an explanation for the aforementioned regioselectivity. The resulting cyclohexadienyl radical intermediate then undergoes one-electron oxidation by PhI(OAc)₂, followed by spontaneous deprotonation. This mechanism is further supported by studies indicating inhibition by radical traps (BHT, TEMPO) and the requirement for two equivalents of oxidant.

Noteworthy are analogous efforts by Antonchick and co-workers,⁷⁴ who at about the same time as the Cho-Chang¹³ and DeBoef⁷² reports, disclosed amidations of simple arenes (2 equiv.) by acetanilides in the presence of PhI(OAc)₂ (1.5 equiv.) in hexafluoroisopropanol (HFIP) (Scheme 26). Only arenes with electron-donating substituents are active. Although no detailed mechanistic data are available for the intermolecular cases, it has been proposed that electrophilic nitrenium ions (R' R'' N⁺; R' = aryl, R'' = acyl), generated by the action of PhI(OAc)₂ on the acetanilide, are the major amidating species.

Organocatalytic versions have been subsequently pursued⁷⁵ in amidations of simple arenes by *N*-methoxybenzamide and hydrazinations by *N*-(1,3-dioxoisindolin-2-yl)acetamide (Scheme 27(a)). Key to the success of these processes is the development of a protocol that uses aryl iodides in catalytic amounts, and relies on sacrificial peracetic acid, along with trifluoroacetic acid, to generate the oxidant in situ. This methodology has been recently extended⁷⁶ to aminations of simple, yet electron-rich arenes (10 equiv.) by various heteroaromatic amines (Scheme 27(b)), either under stoichiometric amounts of PhI(OAc)₂ (1.1 equiv.) in HFIP or HFIP/DCM (1:1) at room temperature, or with catalytic amounts of PhI (25 mol%) and excess AcOOH (5 equiv.).

In a unique example of unusual reactivity, Muñiz and co-workers¹¹ report the metal-free sulfonimidation of a 2-acetylenylaniline in *para* position by the isolable I(III) reagent PhI(NTs)₂ (2 equiv.) in 80% yield (Scheme 28).

(b) Suna's Copper(I)/Diaryl-λ³-Iodane Systems—An elegant one-pot, two-step methodology has been developed by Suna and co-workers⁷⁷ to effect copper-mediated

amination of benzenes by transiently generated unsymmetrical diaryl- λ^3 -iodanes. As opposed to the usually employed sulfonamides, amides and imides, simple amines are easily oxidized by monoaryl- λ^3 -iodanes, but are fairly stable towards the diaryl congeners.

In the first step of the method (Scheme 29), the iodonium reagent $\text{ArI}(\text{OH})\text{OTs}$ (Ar = 2,4,6-trisopropylphenyl (TIPP) or 2,4,6-trimethylphenyl (Mes)), whose electrophilicity is enhanced by the addition of a strong acid (TfOH or TsOH , 1.05 equiv.), reacts with the aromatic substrate in MeCN at room temperature, over a time period necessary for the formation of the corresponding unsymmetrical diaryl- λ^3 -iodane. In a subsequent same-pot step, the amine (1.2 equiv., illustrated for morpholine), a base ($\text{EtN}(i\text{-Pr})_2$, 2.0 equiv.), and the copper(I) catalyst $[\text{Cu}(\text{NCMe})_4]\text{BF}_4$ (10 mol %) are added along with DMSO, to adjust the solvent mixture to 1:4 MeCN:DMSO, and allowed to react for 12 hours at 40 °C to afford the arylamine in moderate to excellent yields (25 – 80 % for selective simple arenes). Even in the presence of a strong acid, the iodonium addition to the aromatic substrate is successful only with benzenes that are more electron-rich than toluene. Furthermore, the TIPP-I(OH)OTs reagent is more effective than the mesityl (Mes) based congener,⁷⁸ because the bulky TIPP is completely nontransferable to the amine from the standpoint of the unsymmetrical diaryl- λ^3 -iodane. Most importantly, the C–N bond formation is highly regioselective, since the intermediate diaryl- λ^3 -iodanes feature *para* substitution with respect to the most electron-releasing substituent of the aromatic substrate. Several prim/sec aliphatic and (hetero)aromatic amines can be employed, as well as ammonium trifluoroacetate, but not ammonia. The protocol is compatible with various functional groups on the aromatic substrate or the amine. Detailed mechanistic data are not available, but the authors favor a key oxidative addition step of the acid-activated diaryl- λ^3 -iodane intermediate to a preformed copper(I)-amine adduct to generate $\text{Cu}^{\text{III}}(\text{aryl})(\text{NR}'\text{R}'')$, leading to product via reductive elimination.

Metal-dependent Arene Imidations

(a) Hartwig's Pd-Mediated System—An interesting elaboration of the metal-free arene imidation work has been reported by Hartwig and co-workers⁷⁹ in the presence of catalytic amounts of $\text{Pd}(\text{OAc})_2/t\text{-Bu}_3\text{P}$ (10 mol%) at 100 °C (Scheme 30). Phthalimides perform best as limiting reagents for the imidation of arenes (neat, 5.0 mL), in the presence of $\text{PhI}(\text{OAc})_2$ added in three portions (2 equiv. each; time intervals: 0, 9, 24 h). Benzene is imidated in low yields (30%), and many mono-substituted benzenes, with electron-donating or electron-withdrawing substituents, are imidated in good to excellent yields, and regioselectivity favoring the sterically less encumbered *meta* and *para* positions with increasing size of the substituent. Similarly, symmetrical and unsymmetrical 1,2- or 1,3-disubstituted and trisubstituted benzenes provide products of imidation at the least hindered position.

Detailed mechanistic pathways for the Pd(II)-mediated, sterically-controlled imidation have not been elucidated, but are certainly distinguishable from those operating in similar arene acetoxylation catalytic systems that are clearly *ortho/para* directing.⁸⁰ A concerted C–H metallation-deprotonation step is favored, supported by sizeable KIE values (4.1 ± 0.1 for benzene/benzene- d_6 ; 2.8 ± 0.1 for 1,2-dichlorobenzene/1,2-dichlorobenzene- d_4).

(b) DeBoef's Gold-Mediated System—Further advances with respect to the regioselectivity of arene phthalimideation have been realized by DeBoef and co-workers,⁸¹ by developing a protocol that employs arene as a solvent (3.0 mL) and phthalimide as the limiting reagent, in the presence of $\text{Cy}_3\text{P-Au-Cl}$ (10 mol%) and an excess of $\text{PhI}(\text{OAc})_2$ (8 equiv., delivered in two equal portions at 0 and 12 h) at 100 °C over 24 hours (Scheme 31(a)).

As is the case with Hartwig's system,⁷⁹ excess oxidant is needed because apparently aryl coupled products are observed. Both electron-donating and electron-withdrawing substituents are imidated, albeit the latter at significantly lower yields (certainly lower than Hartwig's system). Most importantly, the regioselectivity observed is highly favoring the *para* position (as opposed to *meta/para* in Hartwig's system), presumably due to an alternative mode of operation, supported by the absence of a KIE (1.04 for benzene/benzene- d_6). Indeed, the authors favor a standard electrophilic aromatic metallation by Au(III) , which is electronically *ortho/para* directed, but due to the bulk of the metal, auration of the *para* position is preferred (Scheme 31(b)). A certain degree of *meta* activation is also observed, presumably owing to the intervention of low-level, metal-free imidation (as noted in DeBoef's contribution⁷² noted above), especially with electron-deficient arenes, for which electrophilic auration tends to be slow. The role of $\text{PhI}(\text{OAc})_2$ is considered to be dual, first by enabling the oxidation of Au(I) to Au(III) , and further by engaging in transmetallation of the PhthN- moiety from a preformed $\text{PhthN-I}(\text{OAc})\text{Ph}$ to Au(III) (albeit in a redox unbalanced step). Most interestingly, purely synthesized $\text{PhI}(\text{NPhth})_2$ can be used in lieu of phthalimide in the catalytic reaction, together with only one equivalent of $\text{PhI}(\text{OAc})_2$.

(c) Ritter's Pd/Ag(or Ru)-Mediated NFSI-based System—Several research groups have addressed metal-assisted imidation of aromatics with *N*-fluorobenzenesulfonimide (NFSI). Noteworthy are original contributions by Zhang⁸² on the use of NFSI for the amide-directed, palladium-catalyzed C–H amination of *N*-phenylacetamides selectively at the *ortho*, *para*, or benzylic (for *N-p*-tolylacetamides) position. The benzylic amination was further elaborated by Zhang and Liu⁸³ with copper-mediated systems that remarkably favor primary over secondary benzylic sites. These seminal contributions are not reviewed further, since they fall outside the scope of the present review.

Ritter and co-workers⁸⁴ have introduced a bimetallic catalytic system that engages the Pd(II) complex $[\text{Pd}^{\text{II}}(\text{N-(2-pyridylmethyl)pyrrolidine-N-oxide})_2](\text{OTf})_2$ (5 mol %) along with $[\text{Ag}(\text{bipy})_2](\text{ClO}_4)$ (10 mol%) in MeCN at room temperature (Scheme 32). The latter can be substituted by $[\text{Ru}(\text{bipy})_3](\text{PF}_6)_2$ (2.5 mol%) at 50 °C, suggesting that the Ag(I) or Ru(II) complexes act as electron relays. Selective examples of imidation of simple arenes, used as limiting substrates versus NFSI (2 equiv.), indicate that the regioselectivity is substrate dependent, ranging from typical electrophilic aromatic substitution patterns (*ortho/para*) for π -donor substituents to mixtures of *o/m/p* products for inductive donor substituents. Competing fluorination and/or double imidation is observed on occasion, although these undesirable pathways can be minimized by conducting the reaction at 4 °C.

The authors propose a mechanistic scheme (Scheme 33) that is consistent with a handful of experimental data. The catalytic reaction is first-order with respect to the Pd(II) complex and

the NFSI, and zero-order with respect to the Ag(I) complex and the aromatic substrate. The rate constant is essentially the same as that measured for reduction of NFSI to $\text{HN}(\text{SO}_2\text{Ph})_2$ and HF by catalytic amounts of Pd(II) alone. These results suggest that the two-electron oxidative addition of NFSI to Pd(II) is the turnover-limiting step. In a less secure step, Ag(I) (or Ru(II)) is proposed to mediate outer-sphere reduction of Pd(IV) to a crucial Pd(III) intermediate that exhibits π complexation with the arene. The product is generated via attack of the π -complexed arene by the Pd(III)-bound $(\text{PhSO}_2)_2\text{N}$ moiety, presumed to operate as a dibenzenesulfonimidyl radical, in agreement with an inverse intramolecular KIE value (0.80 ± 0.01 , for imidation of 1,3,5-trideuteriobenzene; 1.03 ± 0.02 for benzene/benzene- d_6), followed by oxidation of the resulting delocalized cyclohexadienyl radical by Ag(II) and subsequent deprotonation.

(d) Itami's Cu-Mediated NFSI-Based System—The imidation of a series of extended aromatic substrates by NFSI has been elaborated by Itami and co-workers.⁸⁵ The amination of polycyclic aromatic hydrocarbons has been recently reviewed by the same authors.^{2f} Two simple arenes, benzene and naphthalene, have been included in this study (Scheme 34), and shown to be imidated in modest yields. Benzene is employed in excess (20 equiv.) versus NFSI, but naphthalene is present in limiting amounts (1.3 equiv. of NFSI). The catalyst is assembled by mixing CuBr and 6,6'-Me₂bpy (for benzene: 20/24 mol%; for naphthalene: 10/12 mol %), and the catalytic reaction is conducted in 1,2-dichloroethane at room temperature over 24 hours for benzene, or at 70 °C over 12 hours for naphthalene. Slightly less active catalysts have been obtained with 6-Mebpy or 2,9-Me₂phen. In general, the rate-accelerating effect of one or two methyl substituents of bpy or phen is highlighted. While detailed mechanistic data are not available, the authors propose a turnover-limiting step that involves addition of an electrophilic, metal-bound imidyl radical ($\text{Cu}-\text{N}(\text{SO}_2\text{Ph})_2$) to the arene. By way of analogy to Ritter's results,⁸⁴ an inverse intermolecular kinetic isotope effect (0.91) has been observed for the imidation of 2-phenylthiophene vs. 2-D-5-phenylthiophene.

Arene Aminations by Free Imidyl Radicals

(a) Baran's Ferrocene-Mediated System—Baran and co-workers⁸⁶ have shown that diffusively-free imidyl radicals can be employed as arene imidation agents. Scheme 35 summarizes relevant results that engage selective simple arenes (albeit not mono-substituted aromatics) as limiting reagents, in reactions with a carefully selected *N*-succinimidyl perester (3 equiv.). The perester releases *N*-succinimidyl radicals in the presence of ferrocene (5 mol%) in CH_2Cl_2 at 50 °C, preferably under inert atmosphere.

The methodology is applicable to both electron-rich and electron-deficient arenes and provides products of imidation in good yields and regioselectivities similar to those expected for electrophilic aromatic substitutions. Substitution at *ipso* positions is occasionally observed in low yields. The proposed mechanism is operationally simple (Scheme 36), and involves decomposition of the perester by ferrocene, acting as an electron relay, to generate imidyl radicals that add to the aromatic ring. The delocalized aryl radical is oxidized by FeCp_2^+ , and is subsequently deprotonated to afford the product. Importantly, deprotection in dilute boiling solutions of sulfuric acid can liberate the amine.

(b) Sanford's Ir-based Photocatalytic System—Imidyl radicals can be further generated photochemically and employed for arene imidation, as reported by several research groups. Sanford and co-workers⁸⁷ describe a photocatalytic system (Scheme 37) that relies on visible light in the presence of photocatalyst *fac*-Ir(ppy)₃ (5 mol%; ppy = 2-phenylpyridine) to effect decarboxylative cleavage of *N*-acyloxyphthalimides (RC(O)O–NPhth), affording phthalimidyl radicals (PhthN•) along with CO₂ and carboxylate anion. The electron-withdrawing CF₃C(O)O– moiety is proven to be optimal in generating PhthN• radicals (electron-donating R groups afford the phthalimide anion instead), which can then add to a series of simple arenes (10 equiv.) in MeCN at room temperature over 24 hours in good to excellent yields. The regioselectivity is largely *ortho/para* directing for electron-donating aromatic substituents, but the electron-withdrawing CF₃ favors the *meta* position, albeit with low overall yields.

Detailed mechanistic analysis is not currently available, but the authors propose a typical homolytic (radical) aromatic substitution⁸⁸ mechanism (Scheme 38), involving addition of the electrophilic phthalimidyl radicals to aromatic substrates, supported by standard photoredox steps for the generation of the imidyl radicals and fast quenching of the resulting delocalized cyclohexadienyl radical.

(c) Lee's Ir-based Photocatalytic System—In a very similar study, Lee and co-workers⁸⁹ proceed in further fine-tuning of the conditions, by utilizing *N*-chlorophthalimide as the source of PhthN• radicals, generated via visible light (20 W CFL) coupled with the photocatalyst *fac*-Ir(dFppy)₃, used in only 0.5 mol% (Scheme 39). The presence of additives such as acetic acid (20 mol%) and K₂CO₃ (3 equiv.) give rise to higher product yields, and permit imidation of a wide range of arenes present in a small excess (2.0 equiv.) or even as a limiting reagent (PhthNCl/arene 2:1). Interestingly both electron-donating and electron-withdrawing substituted arenes are imidated in good yields, and with regioselectivities that are not unlike those reported by Sanford.⁸⁷ Benzylic imidation is not observed, although *ipso* substitution occurs to a low extent with MeO-substituted arenes. Furthermore, chlorination rather than imidation is observed with the electron-rich 1,3,5-trimethoxybenzene.

(d) Luo's Metal-free Photolytic System—Finally, Luo and co-workers⁹⁰ report that even *N*-bromo imides can be employed with visible light, but only in the limited case of *N*-bromosaccharin (Scheme 40(a)) that possesses a weak N–Br bond (BDE(calculated): 48 kcal mol^{–1}). For stronger N–Br bonds, such as in PhthN–Br (60 kcal mol^{–1}), UV photolysis is required, which, however, facilitates substrate bromination and benzylic imidation. Interestingly, Luo's system does not require the presence of photocatalyst, and operates on both electron-rich and electron-poor arenes (1.5 or 3.0 equiv.) in CH₂Cl₂ at room temperature, with good yields and surprising predilection for *ortho* and *para* substitution for all substrates examined. The standard homolytic aromatic substitution mechanism is proposed (Scheme 40(b)), with the caveat that, in the absence of a metal oxidant, the Br• radical is employed to quench the incipient cyclohexadienyl radical either by an inner sphere or an outer-sphere process. DFT calculations indicate that the absence of *meta*-substituted

toluene may be explained by an activation free energy that supersedes that for *ortho* or *para* substitution by roughly 1.5 kcal mol⁻¹.

Arene Amination via Initial Aromatic Oxidation

(a) Yoshida's Electrochemical System—Yoshida and co-workers⁹¹ employ a conceptually different approach that relies on electrochemical oxidation of the aromatic substrate (3 – 4.5 F mol⁻¹; divided cell: carbon felt anode, Pt plate cathode, in 0.3 M Bu₄NBF₄, 25 °C) in the presence of excess pyridine (30 equiv.) (Scheme 41(a)). The selective oxidation of the arene to the corresponding radical cation is followed by nucleophilic attack of pyridine and further oxidation/deprotonation, generating an *N*-arylpyridinium ion that is resistant to further oxidation, thus avoiding multiple aminations (Scheme 41(b)). Separate treatment of the anodic mixture with piperidine (10 equiv.) in MeCN at 80 °C yields the corresponding amine in good to excellent yields.

The method is applicable to both electron-rich and electron-deficient arenes and is further compatible with several aromatic substituents (I, NO₂), without signs of benzylic amination. The regioselectivity of the nucleophilic attack is largely *ortho/para* directed and is reportedly guided by the LUMO of the arene radical cation as noted by DFT calculations. In a subsequent publication,⁹² the authors extend this electrooxidative approach to the C–N coupling of protected imidazoles (especially *N*-methylsulfonylimidazole) with arenes. Protection is necessary to avoid overoxidation, leading to undesirable multiple aminations. However, significant benzylic activation is obtained in this case.

(b) Nicewicz's Photooxidation System—The principles of Yoshida's work are further elaborated in a report by Nicewicz and co-workers,⁹³ that introduces a multicomponent system for the amination of aromatics (Scheme 42). First, a 455 nm LED is coupled with an acridinium photocatalyst (5 mol%) to effect oxidation of the arene, as limiting reagent, to the corresponding arene radical cation. Several azoles (1.25 – 2.0 equiv.) are employed (illustrated with pyrazole) to perform nucleophilic attack onto the aromatic radical cation, resulting in an incipient distonic cation radical. This is deprotonated and further quenched by catalytic amounts of TEMPO (20 mol%), apparently via H-atom abstraction, to effect oxidative aromatization, leading to product. Most importantly, the overall system requires dioxygen as a sacrificial two-electron, two-proton sink, affording peroxide. Apparently, dioxygen and superoxide (O₂⁻) act as regenerators of the acridinium- and TEMPO-cycle related oxidants, respectively. The photocatalytic reaction operates in 1,2-dichloroethane at 33 °C, and provides good to excellent yields of aminated arenes. Monosubstituted aromatics direct to *ortho/para* amination exclusively, as noticeable in the Yoshida study.⁹¹ Benzylic amination can be circumvented by eliminating dioxygen and elevating the amount of TEMPO to one equivalent. Finally, ammonium carbamate, (NH₄)(H₂NCO₂), a practical ammonia substitute, can be used in lieu of azoles (4 equiv. over arene) to effect synthesis of anilines under the same protocol.

5. Conclusions

The examples discussed in this paper indicate that significant advances have been achieved in developing catalytic and stoichiometric amination systems for the intermolecular

functionalization of challenging light alkanes and simple aromatics. Naturally, intramolecular versions of sp^3 and sp^2 -C–H aminations are more numerous.^{94–100} Nevertheless, important issues remain unresolved, especially for light alkanes, for which C–H bond activation is frequently the turnover-limiting step. Exceptionally electrophilic metal-bound or metal-free nitrogen-donor carriers are needed to accomplish this goal, due to the strength and low polarity of the C–H bond in these unfunctionalized alkanes. Alternatively, H-atom abstraction from the C–H sites of interest can be relegated to diffusively-free oxygen-centered radicals (such as alkoxy radicals), and the resulting carbon-centered radicals can be captured by nitrogen-group moieties, potentially following pre-coordination of both entities at suitable metal sites. These methodologies are further confronted by challenges with regards to C–H bond selectivity issues (chemo- or regio-selectivity) that naturally tend to favor more electron-rich C–H bonds, but could also be affected by steric hindrance. Novel alkane amination protocols that demonstrate enhanced activity and selectivity are thus in need, and those could benefit from better mechanistic clarity with respect to metal- and substrate-bound events. Moreover, methodologies are in demand that rely on metal-centered C–H activation processes, followed by carbon-group amination, since those may have better chances to reach primary C–H sites. Furthermore, methods to generate stereoselective carbon sites, in tandem with C–N bond formation, will certainly receive more attention in due course.

Examples of intermolecular amination of unfunctionalized aromatics are more numerous, presumably owing to slightly more advantageous thermodynamics, but most importantly due to the availability of several kinetic pathways for the addition of a metal-bound or metal-free nitrogen-group moiety to an aromatic ring (for instance, electrophilic aromatic substitution, homolytic aromatic substitution, oxidatively-promoted nucleophilic aromatic substitution). This felicitous situation is however accompanied by mechanistic uncertainty hence more precise diagnostic tools will be needed to assist in deciphering positional selectivities and other mechanistic data. Efforts to address amination of frequently unreactive electron-poor arenes and further avoid large excesses of aromatic substrate will certainly intensify in the future. Similarly, expansion of the nitrogen-group sources is required, to include N-substituents that are not solely electron deficient, and even furnish direct installment of –NH₂ and –NR₂ functionalities.

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Scheme 1.

Metal-bound and Metal-free Nitrogen-Group Donors Involved in C-H Amination

Scheme 2.
 Amination of Methane and Benzene by Ammonia

Scheme 3.

(a) Thermal Amination of Cyclohexane by Organic Azides. (b) Thermal Amination of 2-Methylbutane by Tosyl Azide. (c) Thermal Amination of 2-Methylbutane by Carboxy Azide. (d) Thermal Amination of Benzene and *para*-Substituted Benzenes by MeSO₂N₃. (e) Mechanism of Singlet Nitrene Addition to Benzenes

Scheme 4.

(a) Reaction of Benzenes with 2-Dimethylchloramide. (b) Addition of Dialkylamino Radical Cations to Benzenes. (c) Catalytic Reaction of Benzenes with Hydroxylamine-*O*-sulfonic acid

		1	2	3	4	
Catalyst ^a	Total Yield (%)	$\frac{1+2}{3+4}$	Relative Proportion (%)			
Mn(TPP)Cl	5	1.70	9	54	19	18
Mn(TPP)OTf	10	1.94	13	52	18	17
Mn(TMP)OTf	NR ^b	4.0	46	34	11	9
Mn(TTMPP)Cl	5	2.45	21	50	15	14
Mn(TDCPP)OTf	13	2.70	26	47	14	13
Fe(TPP)Cl	3	2.85	8	66	14	12
Fe(TPP)OTf	6	3.17	12	64	13	11
Fe(TDCPP)OTf	9	3.35	16	61	12	11

^aTPP = tetraphenylporphyrin; TMP = tetramesitylporphyrin; TTMPP = tetra-2,4,6-trimethoxyphenylporphyrin; TDCPP = tetra-2,6-dichlorophenylporphyrin. ^bNot reported.

Scheme 5.

Mansuy's Mn/Fe-Porphyrin Catalyzed Amination of Heptane by PhI=NTs

Scheme 6. He's Disilver(I) Catalyzed Amination of 2-Methylpentane by PhI=NNs

	PhI=NTs (1 equiv.) Ag catalyst (5 mol%) 80 °C, 4 h		Relative Proportions of Products (%)			Total Yield (%)	Ag Catalyst
	neat (5.0 mL)

		7	58	35	40		Tp*Ag	(R ¹ = R ³ = Me; R ² = H)
		10	59	31	65		Tp*,BrAg	(R ¹ = R ³ = Me; R ² = Br)
		15	53	32	40		Tp ^{Ms} Ag	(R ¹ = R ² = H; R ³ = Mes)
nd	70	30	15		Tp ^{Br3} Ag	(R ¹ = R ² = R ³ = Br)

		5	58	37	40		Tp*Ag	
		5	60	35	70		Tp*,BrAg
15	53	32	35		Tp ^{Ms} Ag	
		nd	72	28	10		Tp ^{Br3} Ag

		>99			65		Tp*Ag
>99			75		Tp*,BrAg	
		>99			25		Tp ^{Ms} Ag	
		>99			10		Tp ^{Br3} Ag	
		>99
40		Tp*Ag	
		91	9					
		90	10		80		Tp*,BrAg	
		76	24		15		Tp ^{Ms} Ag
78	22		8		Tp ^{Br3} Ag	

Scheme 7.

Pérez's Ag(I) Catalyzed Amination of Alkanes by PhI=NTs

Scheme 8.

Pérez's and Müller/Dodd/Dauban's Ag(I) and Rh(II) Catalyzed Comparative Amination of Alkanes by (*S*)-*N*-(*p*-Toluenesulfonyl)-*p*-toluenesulfonimidamide

Scheme 9.

Che's Ru(IV) Catalyzed Amination of Hexane by a Phosphoryl Azide

Scheme 10.

Cu(I) Catalyzed Amination/Amidination of 2-Methylbutane by PhI=NTs

Scheme 11.
Proposed Mechanistic Steps for the Copper-Catalyzed Amination of 2-Methylbutane

				Total Yield (%)	Relative Proportion (%)
	 600-800 equiv.		 NHTf	55	43:57
			 NHTf	72	94:6
			 NHTf	78	
			 NHTf	96	86:14
			 NHTf	64	97:3
			 NHTf	0	
			 NHTf	91	97:3

Scheme 12.Ochiai's Metal-free Amination of Alkanes by a Sulfonylimino- λ^3 -Bromane

(b) Mechanistic Proposal:

Scheme 13.

(a) Hartwig's Cu(I) Catalyzed Amidation of Alkanes by PhCONH₂ in the Presence of di-*tert*-Butyl Peroxide. (b) Proposed Mechanism

(+ TsNH₂ + "poorly soluble oligomers")

(+ "sulfonated oligoarylamines")

Sadighi's Cu(I) Catalyzed Amination of Methoxy-substituted Benzenes by PhI=NTs

(b) Proposed Mechanism by Bao et al.:

Scheme 16.

Pérez's Cu(I) Catalyzed Amination of Benzene, Chlorobenzene and Pyridine by PhI=NTs.

(b) Bao's Proposed Mechanism for the Cu(I) Catalyzed Amination of Benzenes

Scheme 17.

He's Au(III) Catalyzed Amination of Benzenes by PhI=NNs

Scheme 18.

Bao-Schaefer's Computational Mechanistic Interpretation of He's Gold(III) Catalyzed Aromatic Amination of Mesitylene by PhI=NNs

Scheme 19.

Zhang's Au(III) Catalyzed Amination of Benzenes by Azodicarboxylates

Scheme 20.

Zhang's Proposed Mechanism for the Au(III) Catalyzed Amination of Benzenes by Azodicarboxylates

Scheme 21.

Jensen's Fe(II) Catalyzed Amination of Benzenes by PhI=NTs

Scheme 22. Nicholas' Cu(I) Catalyzed Amidation of Benzenes by *N*-Tosyloxyltrichloroethylcarbamate

Scheme 23.

Cho-Chang's Metal-free Imidation of Benzenes by Phthalimide in the Presence of PhI(OAc)₂

Scheme 24. DeBoef's Metal-free Imidation of Benzenes by Phthalimide in the Presence of $\text{PhI}(\text{OAc})_2$

Scheme 25.

DeBoef's Proposed Mechanism for the Oxidative Imidation of Toluene by Phthalimide

Selective Products

Scheme 26.

Antonchick's Metal-free Amidation of Benzenes by Acetanilides in the Presence of $\text{PhI}(\text{OAc})_2$

Scheme 27.

(a) Antonchick's Organocatalytic Oxidative Amidation and Hydrazination of Benzenes. (b) Organocatalytic Oxidative Amination of Benzenes by Heteroaromatic Amines

Scheme 28. Muñiz's Metal-free Sulfonimidation of 2-Acetylenylaniline by $\text{PhI}(\text{NTs}_2)_2$

Scheme 29.

Suna's Two-step One-pot Cu(I) Catalyzed Amination of Benzenes via Intermediate
 Unsymmetrical Diaryl- λ^3 -Iodanes

Scheme 30.

Hartwig's Pd(II) Catalyzed Imidation of Benzenes by Phthalimide

Scheme 31.

(a) DeBoef's Au(I) Catalyzed Imidation of Benzenes by Phthalimide. (b) Proposed Mechanistic Steps

Scheme 32.

Ritter's Pd(II)/Ag(I) (or Ru(II)) Catalyzed Imidation of Benzenes by NFSI

Scheme 33.

Ritter's Mechanism for the Imidation of Mono-substituted Benzenes by NFSI, Mediated by a Bimetallic Pd(II)/Ag(I) Catalytic System

Scheme 35. Baran's Ferrocene Catalyzed Imidation of Benzenes by *N*-Succinimidyl Radicals

Scheme 36.

Baran's Proposed Mechanism for the FeCp₂ Catalyzed Imidation of Benzenes by *N*-Succinimidyl Radicals

Scheme 37.

Sanford's Ir(III) Mediated Imidation of Benzenes by Photocatalytically Generated Phthalimidyl Radicals

Scheme 38.

Sanford's Proposed Mechanism for the Ir(III) Mediated Imidation of Benzenes by Photocatalytically Generated Phthalimidyl Radicals

Scheme 39.

Lee's Ir(III) Mediated Imidation of Benzenes by Photocatalytically Generated Phthalimidylyl Radicals

Scheme 40.

(a) Luo's Metal-free Imidation of Benzenes by Photolytically Generated *N*-Saccharin Radicals. (b) Proposed Mechanism

(a)

X	Yield	<i>o/p</i> (%)
OMe	69%	0: 100
OPh	92%	43: 57
Ph	71%	0: 100

X	Yield	<i>rel. ratio</i> (%)
Me	74%	100: 0
I	81%	100: 0
COOMe	92%	70: 30
COPh	66%	100: 0

97% (*rel. ratio* 66: 34)

84%

95% (*rel. ratio* 70: 30)

(b) Proposed Mechanistic Steps (C–N bond formation)

Scheme 41.

(a) Yoshida's Amination of Benzenes via Electrochemical Oxidation of the Aromatic Substrate. (b) Proposed Mechanism

Selective Products

X	Yield	<i>o/p</i>
OMe	88%	1: 8.8
OMOM	52%	1: 7.8
OTBS	74%	1: 9.3
<i>Ot</i> -Bu	63%	1: 6
OPh	86%	1: 11
Ph	56%	1: 7.9

(b) Proposed Mechanism

Scheme 42.

(a) Nicewicz's Amination of Benzenes by Pyrazole Mediated by Oxygen-dependent Photoredox Catalysis. (b) Proposed Mechanism