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A Three-Component, Interrupted Radical Heck/Allylic Substitution Cascade Involving Unactivated Alkyl Bromides

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Supporting Information Placeholder

ABSTRACT: Developing efficient and selective strategies to approach complex architectures containing (multi-)stereogenic centers has been a long-standing synthetic challenge in both academia and industry. Catalytic cascade reactions represent a powerful means of rapidly leveraging molecular complexity from simple feedstocks. Unfortunately, carrying-out cascade Heck-type reactions involving unactivated (tertiary) alkyl halides remains an unmet challenge owing to unavoidable β-hydride elimination. Herein, we show that a modular, practical and general palladium catalyzed, radical three-component coupling can indeed overcome the aforementioned limitations through an interrupted Heck/allylic substitution sequence mediated by visible light. Selective 1,4-difunctionalization of unactivated 1,3-dienes, such as butadiene, has been achieved by employing different commercially available nitrogen-, oxygen-, sulfur- or carbon-based nucleophiles and unactivated alkyl bromides (>130 examples, mostly >95:5 *E/Z*, >20:1 rr). Sequential C(sp^3)–C(sp^3) and C–X (N, O, S) bonds have been constructed efficiently with a broad scope and high functional group tolerance. The flexibility and versatility of the strategy has been illustrated in a gram-scale reaction and streamlined syntheses of complex ether, sulfone and tertiary amine products, some of which would be difficult to access *via* currently established methods.

1. Introduction

The selective construction of carbon–carbon and carbon–heteroatom bonds is a key transformation in drug discovery and synthesis of medicinally relevant scaffolds.[1] Transition metal catalyzed cross-coupling reactions, such as the Suzuki-Miyaura, Negishi and Mizoroki-Heck reaction have become well-established tools in the formation of these bonds, leading to the award of the 2010 Nobel Prize in Chemistry (**Scheme 1a**).[2]

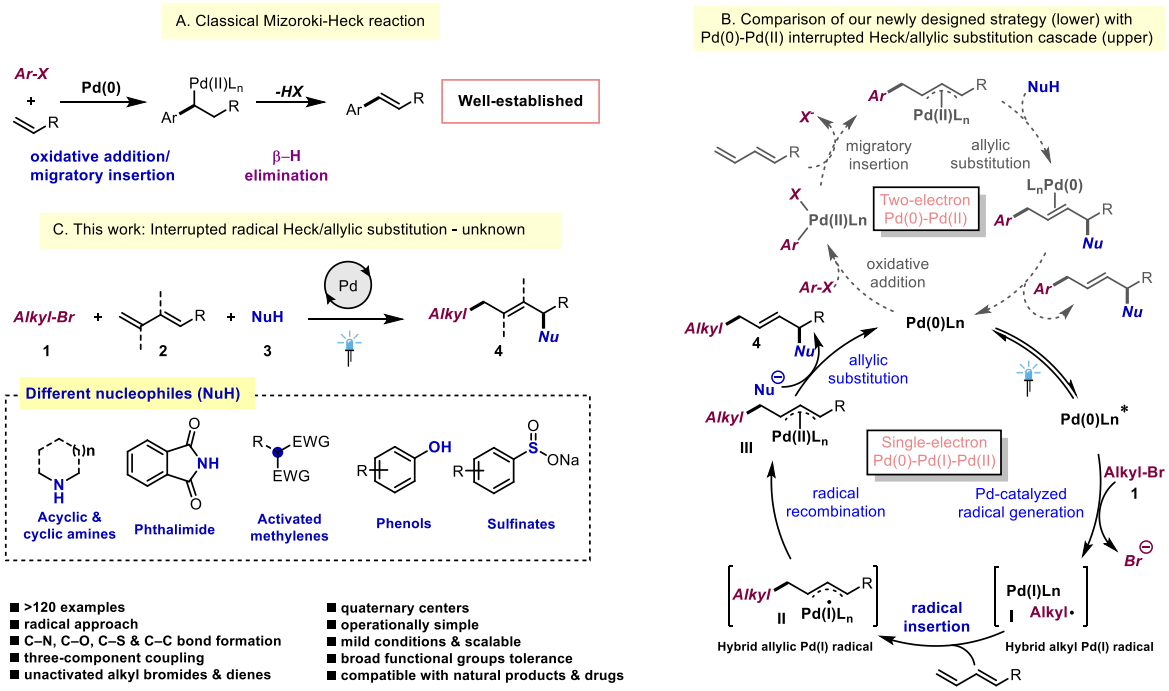
Catalytic cascade reactions, which allow the *de-novo* synthesis of structurally complex architectures from readily available precursors, have been recognized as a pivotal synthetic strategy in organic chemistry.[3] For example, palladium-catalyzed cascade reactions involving Heck–type processes represent a prominent methodology for accessing the multi-functionalization of π–systems.[4] Typically, this sequential transformation is initiated by the oxidative addition of palladium (0) to a vinyl or aryl halide, followed by a reaction of the palladium (II) intermediate with another coupling partner. Meanwhile, palladium catalyzed allylic substitution reactions (the well-known *Tsuji-Trost* reaction) are also frequently used synthetic methods to achieve nucleophilic allylic functionlization.[5] The concept of merging Heck reaction with allylic substitution in one synthetic platform was conceived and admirably achieved as early as in 1978 by Heck.[6] Later on, several groups such as Dieck,[7] Larock,[8] Tsuji,[9] Sigman,[10] Gong[11] and others[12] have developed elegant examples of three-component arylative or vinylative allylic substitution of 1,3-dienes. Combining the Heck reaction with allylic substitution has appeared as a unique strategy to achieve the difunctionalization of 1,3-dienes with only catalytic amounts of palladium through oxidative addition, migratory insertion and allylic substitution (**Scheme 1b**, up). Despite the synthetic utility of these processes, interrupted Heck/allylic substitution cascades have traditionally been limited to activated or sp^2-hybridized aryl or vinyl electrophiles.[12]

To overcome this significant synthetic drawback, we considered that a radical strategy could be an alternative approach to achieve an interrupted Heck/allylic substitution cascade involving sp^3-hybridized aliphatic electrophiles. Pioneered by Fu,[13] Alexanian,[14] Weix,[15] Zhou,[16] Gong[17] and others,[18] *unactivated* alkyl halides have been employed in C–C and C–X bond-forming cross-coupling reactions.[19] Palladium-catalyzed Heck reactions featuring *unactivated* alkyl halides mediated by visible light[20] have been achieved by the groups of Shang and Fu,[18a] Gevorgyan[18c] Rueping[18h] and Yu[18i]. Inspired by recent achievements in palladium-catalyzed radical reactions,[21] we hypothesized that a hybrid alkyl Pd(I) radical intermediates **I**, generated from unactivated tertiary alkyl bromides **1** by

photoinduced palladium catalysis,[18c,18h,18i] could undergo radical addition into 1,3-dienes to form hybrid allylic Pd(I) radical species **II**. Then, after radical recombination, π-allylpalladium complexes **III** could be generated. Different nucleophiles could potentially be employed to attack the intermediate **III** to form the product **4** and regenerate the palladium catalyst without additional oxidants or reductants (**Scheme 1b**, below).

Radical cross-coupling (RCC) offers a unique manner of constructing ubiquitous C(sp^3)–C(sp^3) bonds in a controlled fashion, orthogonal to traditional cross-coupling methodology.[22] This said, radical three-component couplings involving *unactivated* alkyl halides remain rare.[23] Herein, we present the successful development of a modular, radical, three-component coupling that achieves an interrupted Heck/allylic substitution cascade involving *unactivated* alkyl halides which, *to the best of our knowledge*, is unknown (**Fig 1c**). This innovation could open new opportunities to discover novel reactions, accelerate drug and advanced materials discovery and is complementary to current palladium catalyzed cascade reactions which proceed through ionic mechanisms. Sequentially, a C(sp^3)–C(sp^3) bond and a C–X (X = N, O, S, C) bond have been constructed selectively in excellent yields as well as complete regio-, and diastereoselectivities (>120 examples, mostly >95:5 dr, >20:1 rr). Indeed, complex aryl-ether, sulfone and amine products could be formed in a single step from widely available starting materials.

Scheme 1. Radical approaches applied in the interrupted Heck/allylic substitution cascade. a) Classic Mizoroki-Heck reaction; b) Comparison of our newly designed radical strategy involving a Pd(0)–Pd(I)–Pd(II) (lower) with a Pd(0)-Pd(II) interrupted Heck/allylic substitution processes (upper); c) This work: radical three-component coupling: interrupted Heck/allylic substitution cascade involving unactivated alkyl halides

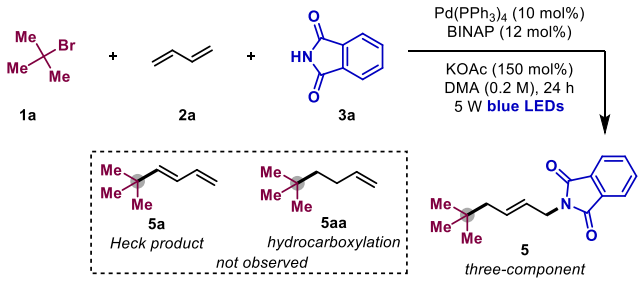


2. Results and discussion

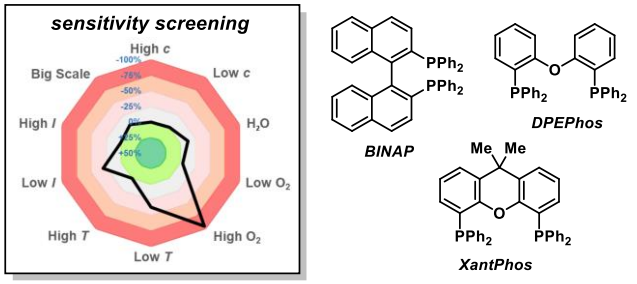
2.1 Reaction design and optimization

Previously, we developed a two-component reaction between *N*-hydroxyphthalimide (NHP) esters and 1,3-dienes.[24] However, the scope of nucleophile was limited to the liberated phthalimide, as addition of other nucleophiles had invariably led to a mixture of products. Based on the concept that we proposed in **Scheme 1b**, we began our work by evaluating the radical three-component coupling *via* combination of the commercially available *tert*-butyl bromide (**1a**), feedstock 1,3-butadiene (**2a**)[25] and phthalimide (**3a**) (**Table 1**). After careful evaluation of all reaction parameters, we found that a combination of $Pd(PPh_3)_4$ (10 mol%), BINAP (12 mol%) and KOAc (150 mol%) in DMA at room temperature under irradiation with blue LEDs provided the three-component coupling product **5** in 60% yield and excellent selectivity (>95:5 dr and >20:1 rr, entry 1). The use of XantPhos or DPEPhos instead of BINAP provided a decreased yield of **5** (entries 2-3). Both the use of different bases and running the reaction in the absence of BINAP were attempted, but all resulted in a decreased yield (entries 4-5). Pleasingly, longer reaction times (48 h) increased the yield to 87% (isolated) (entry 7). Lowering the catalytic amount of $Pd(PPh_3)_4$ and BINAP decreased the yield of the three-component coupling product **5** (73%, entry 8). Control experiments indicated that all the components were essential to form the sequential C(sp^3)–C(sp^3) and C-N linkage (entries 6, 9-12). Condition-based sensitivity screening[26] was also performed, indicating that the reaction is sensitive towards low light intensity, low temperature and high oxygen concentration. The process was scaled-up by a factor of 20 without significant erosion in yield.

Table 1. Optimization of three-component interrupted radical Heck/allylic substitution cascade[a]



Entry	Deviation from standard conditions	5 (%)[b,c]
1	*None*	60
2	DPEPhos instead of BINAP	51
3	XantPhos instead of BINAP	17
4	Na_2CO_3, $NaHCO_3$, K_2HPO_4 instead of KOAc	17 *or* 5 *or* 0
5	without BINAP	31
6	without BINAP and KOAc	0
7	**48 h**	**91 (87)**[d]
8	$Pd(PPh_3)_4$ (5 mol%)/BINAP (6 mol%), 48 h	73
9	without $Pd(PPh_3)_4$, 48 h	-
10	4-CzIPN (5 mol%) instead of $Pd(PPh_3)_4$, 48 h	-
11	without blue LEDs, 48 h	-
12	100 °C instead of blue LEDs, 48 h	<5



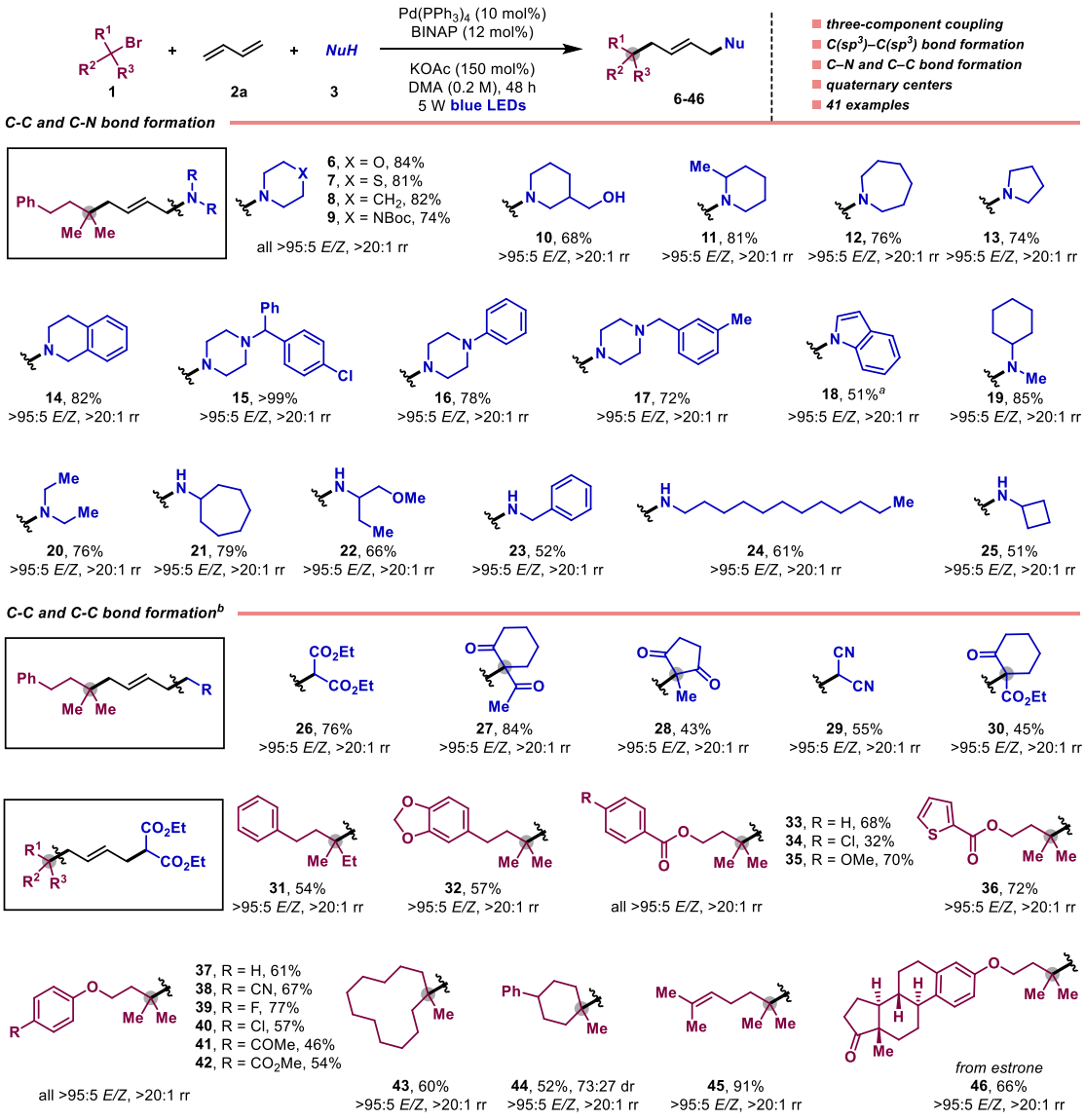
[a] **1a** (0.3 mmol), $Pd(PPh_3)_4$ (10 mol%), ligand (12 mol%), butadiene **2a** (0.3 mmol, 2 *M* in THF, 0.15 mL), DMA (0.85 mL), **3a** (0.2 mmol), base (0.3 mmol), RT, blue LEDs (5 W, 455 nm), 24 h, under argon. [b] Yield was determined by ^{1}H NMR spectroscopy analysis with 1,2-dibromoethane as internal standard. [c] >95:5 dr and >20:1 rr in all cases determined by ^{1}H NMR spectroscopy at the crude reaction mixture. [d] Isolated yields.

2.2 Three-component coupling of an interrupted radical Heck/allylic substitution cascade

With the optimized conditions in hand, we next studied the applicability of our catalytic, interrupted radical Heck/allylic substitution cascade reaction (**Schemes 2–4**). Firstly, different nitrogen-based nucleophiles were examined (**Scheme 2**) and revealed that the three-component reaction could be extended to nucleophiles other than phthalimide. Commercially available morpholine (**6**), thiomorpholine (**7**), piperidines (**8**, **10–11**), piperazines (**9**, **15–17**), azepane (**12**), pyrrolidine (**13**), 1,2,3,4-tetrahydroisoquinoline (**14**), indole (**18**), acyclic secondary amines (**19–20**) and primary amines (**21–25**) were all tolerated in this three-component coupling with moderate to excellent yields (51% to >99%). Pleasingly, the presence of other polar motifs such as alcohols did not interfere neither with productive C(sp^3)-C(sp^3) coupling nor C-N bond formation (**10**). Different carbon-based nucleophiles including diethyl malonate (**26**), substituted cyclohexanones (**27** & **30**), substituted 1,3-cyclopentanedione (**28**) and malononitrile (**29**) could also be employed as coupling partners. Additionally, a range of unactivated tertiary alkyl bromides (**31-46**) was also examined in the three-component coupling with diethyl malonate as nucleophile. Notably, esters (**33–36**), ethers (**37–42**, **46**), alkenes (**45**), ketones (**46**), carbocycles (**43–44**), heterocycles (**36**) and estrone (**46**) were all well tolerated, demonstrating an excellent functional group tolerance of this process.

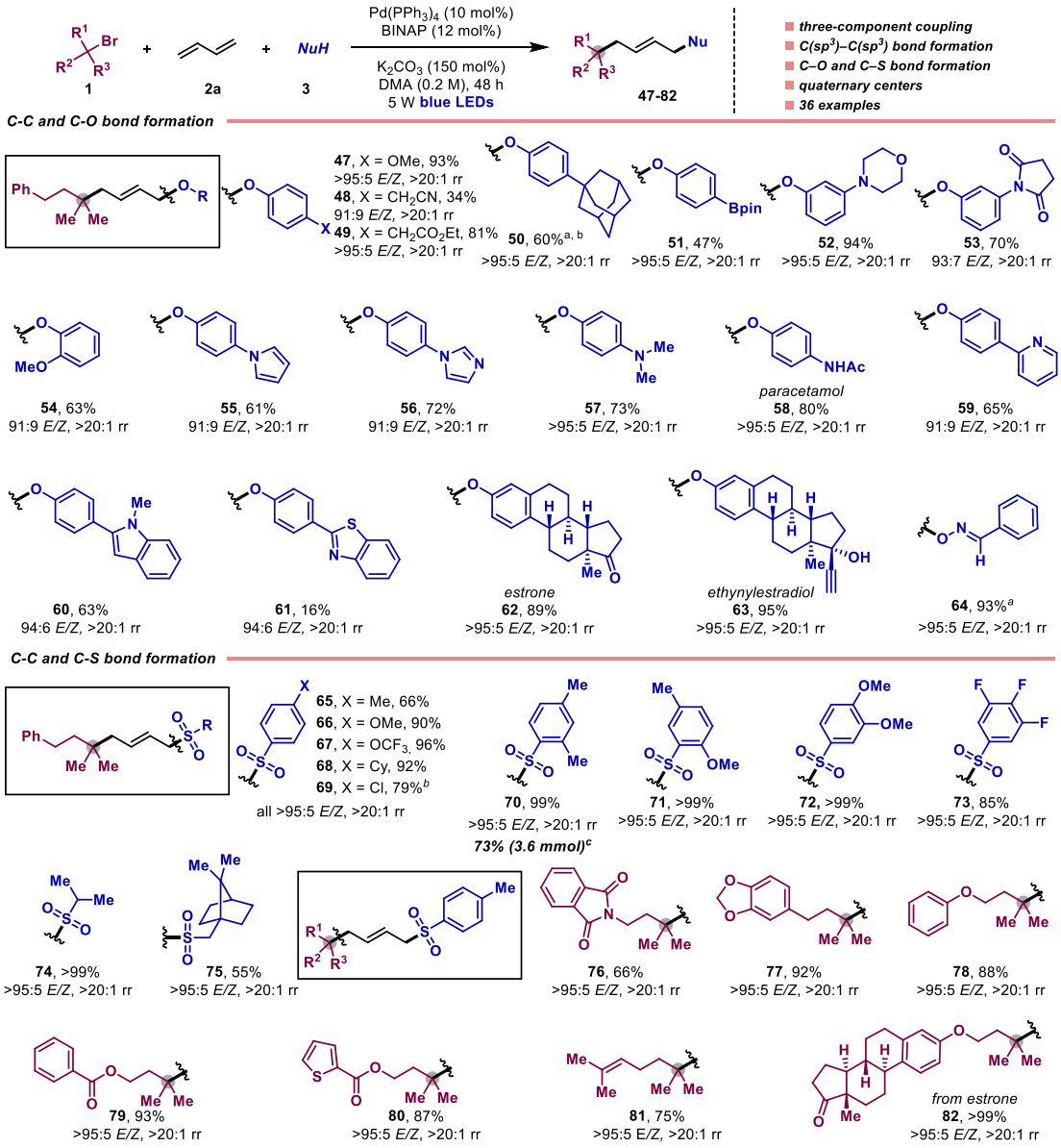
Interestingly, by simple tuning of the pK_a of the base, oxygen- and sulfur-based nucleophiles could be successfully employed in this radical three-component coupling (**Scheme 3**). As shown, the manifold provided the desired product in presence of methoxy (**47** & **54**), nitrile (**48**), ester (**49**), adamantane (**50**), morpholine (**52**), imide (**53**), amine (**57**), and amide (**58**) decoration on the phenol moiety. Notably, pinacol borates (**51**) were well-accommodated, thus opening broad opportunities for further transformation *via* conventional cross-coupling reactions. Remarkably, medicinally interesting motifs such as pyrrole (**55**), imidazole (**56**), pyridine (**59**), indole (**60**), benzothiazole (**61**) and complex drug molecules (estrone **62**; ethynylestradiol **63**) could also be used as coupling partners. Moreover, an oxime (**64**) could also be employed, affording the corresponding *O*-alkylated compound. Sulfinate salts are useful and versatile synthetic intermediates that provide access to medicinally relevant architectures.[27] Particularly, sulfinates are among the intermediates of choice in drug discovery, to promote rapid exploration of structure-activity relationships, owing to their synthetic versatility. Again, a whole spectrum of functional groups such as methoxy (**66, 71-72**), trifluoromethoxy (**67**), chloride (**69**), fluoro (**73**) and aliphatic sulfinate (**74** & **75**) all produced the corresponding three-component coupling product in good to excellent yields (55% to >99%). Furthermore, several important functional groups, including imide (**76**), ether (**78**), ester (**79-80**), thiophene (**80**), alkene (**81**), ketone (**82**), were preserved during the transformation.

Scheme 2. Radical three-component coupling with nitrogen and carbon-based nucleophiles



Reaction conditions: **1** (0.3 mmol), **3** (0.2 mmol), $Pd(PPh_3)_4$ (10 mol%), BINAP (12 mol%), butadiene **2a** (0.3 mmol, 2 *M* in THF, 0.15 mL), DMA (0.85 mL), KOAc (0.3 mmol), RT, blue LEDs (5 W, 455 nm), 48 h, under argon. [a] NaOH (150 mol%) was used instead of KOAc. [b] **1** (0.2 mmol, 1.0 equiv.), **3** (0.6 mmol, 3.0 equiv.).

Scheme 3. Radical three-component coupling with oxygen- and sulfur-based nucleophiles

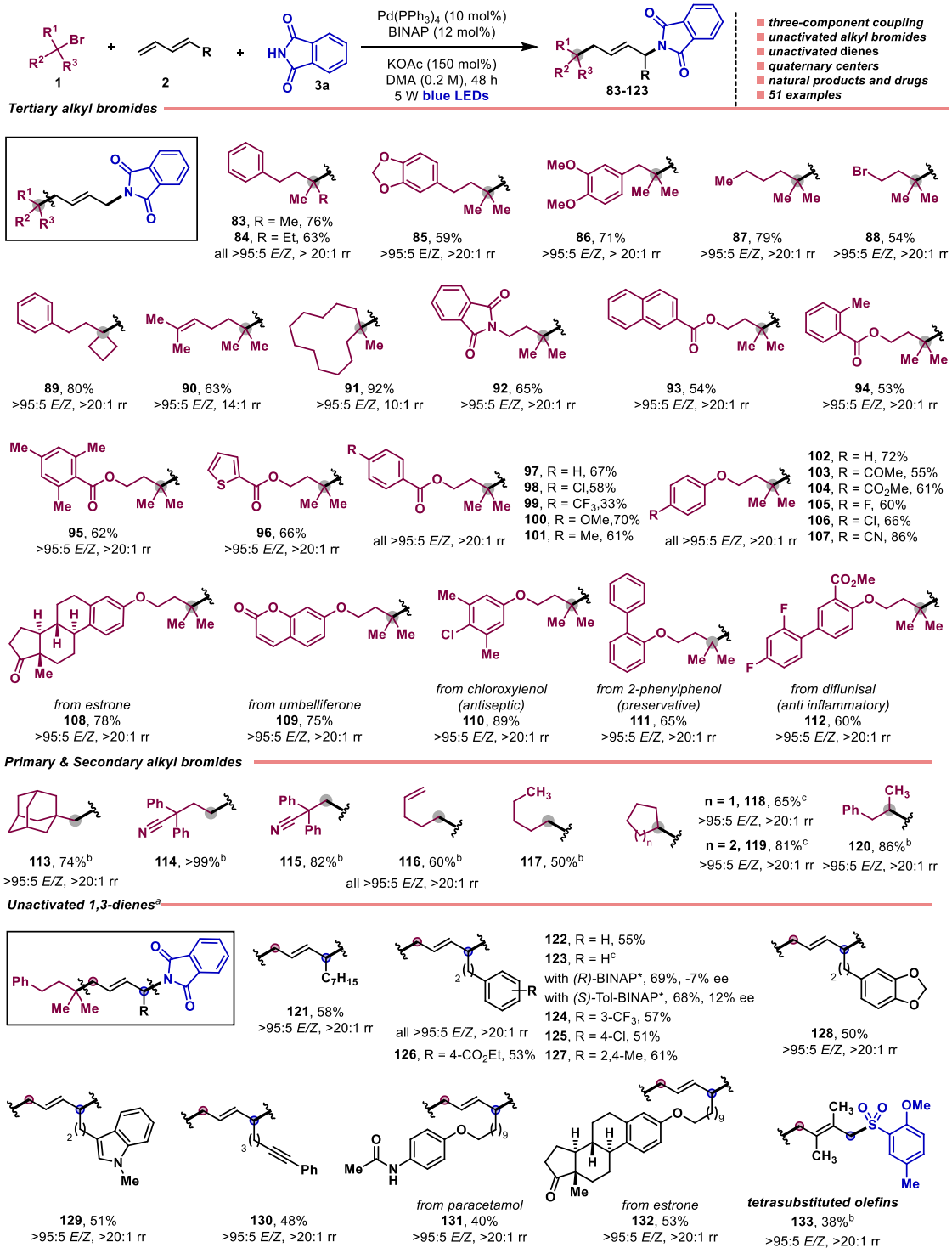


Reaction conditions: **1** (0.3 mmol), **3** (0.2 mmol), $Pd(PPh_3)_4$ (10 mol%), BINAP (12 mol%), butadiene **2a** (0.3 mmol, 2 *M* in THF, 0.15 mL), DMA (0.85 mL), KOAc (0.3 mmol), RT, blue LEDs (5 W, 455 nm), 48 h, under argon. [a] $PhthCH_2CH_2(CH_3)_2Br$ was used. [b] Yield was determined by ^1H NMR spectroscopy analysis with 1,2-dibromoethane as internal standard. [c] The conditions were modified as following: **1b** (1.3 equiv.), $Pd(PPh_3)_4$ (5 mol%), BINAP (6 mol%), 48 h.

With a reliable set of conditions in hand for nitrogen-, oxygen-, sulfur- and carbon-based nucleophiles and feedstock 1,3-butadiene, we wondered whether our protocol could be applied within the context of different unactivated tertiary alkyl bromides (**Scheme 4**). Notably, the catalytic manifold proved to work in the presence of methoxy (**85** & **86** & **100**), cycloalkanes (**89** & **91**), alkene (**90**), imide (**92**), esters (**93**-**101**), ethers (**102**-**112**), heterocycles (**96** & **109**), chlorides (**98** & **106**), trifluoromethyl (**99**), fluoro (**105**), ketone (**103**), nitrile (**107**). The reaction could also be extended to drug and natural product derived unactivated tertiary alkyl bromides which included estrone (**108**), umbelliferone (**109**), chloroxylenol (**110**), 2-phenylphenol (**111**) and diflunisal (**112**). To our delight, the protocol could also employ primary (**113**-**117**) and secondary (**118**-**120**) bromides as radical precursors. Primary radicals featuring long-chain alkane (**117**), terminal alkene (**116**), adamantyl (**113**) and nitrile (**114, 115**) afforded the desired product in excellent stereo- and regioselectivity as well as five- (**118**), six-membered (**119**) and acyclic (**120**) secondary radicals. Regretfully, benzyl bromides and α-bromoesters proved unreactive under the optimized conditions. Finally, we wondered whether our protocol could be applied to unactivated 1,3-dienes apart from 1,3-butadiene. Remarkably the site-selective difunctionalization of substituted 1,3-dienes was accompanied by excellent regioselectivity. Scaffolds that included aliphatic (**121**), aromatic (**122**-**127**), heterocyclic (**128**-**129**), al-

kyne (**130**), trifluoromethyl (**124**), chloride (**125**), ester (**126**), indole (**129**), amide (**131**), ether (**131** & **132**), ketone (**132**) and complex estrone-containing motifs (**132**) could be formed efficiently. While the use of enantiopure ligands (**123**) delivered minimal enantiomeric enrichment, we were pleased to observe that 2,3-disubstituted dienes proved suitable to generate challenging tetrasubstituted olefins in stereocontrolled fashion (**133**).[28] The stereochemistry was assigned as *E* utilizing 1D-NOESY and based upon steric grounds.

Scheme 4. Radical three-component coupling with unactivated alkyl bromides and 1,3-dienes



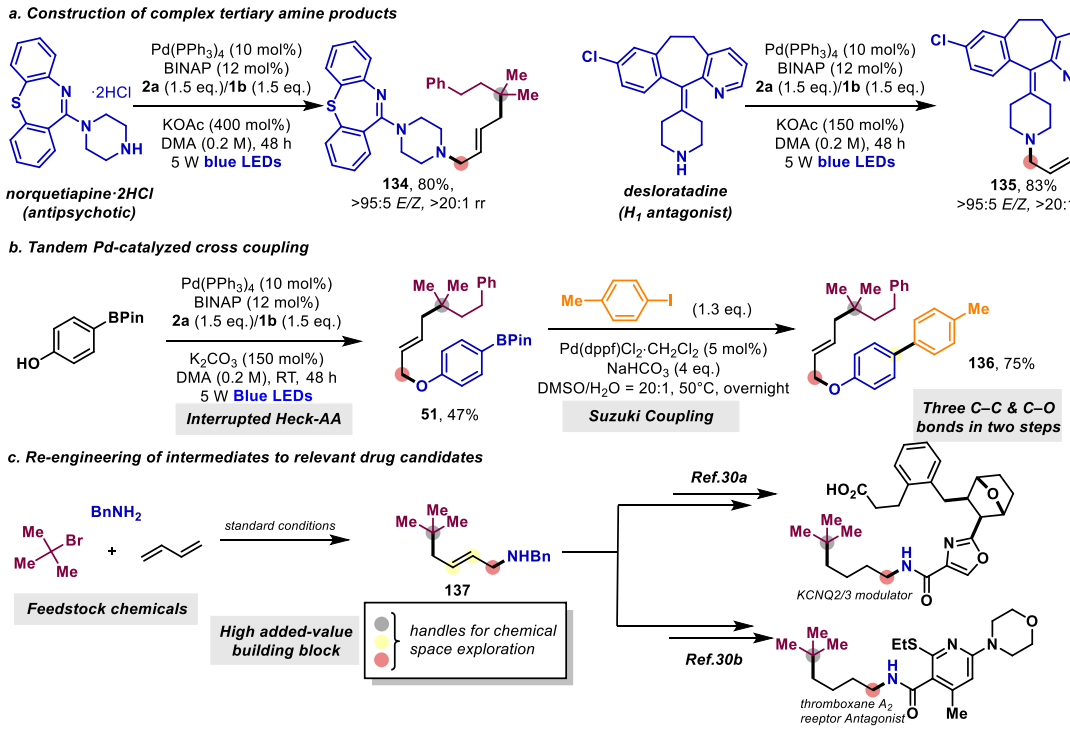
Reaction conditions: **1** (0.3 mmol), **3a** (0.2 mmol), $Pd(PPh_3)_4$ (10 mol%), BINAP (12 mol%), butadiene **2a** (0.3 mmol, 2 *M* in THF, 0.15 mL), DMA (0.85 mL), KOAc (0.3 mmol), RT, blue LEDs (5 W, 455 nm), 48 h, under argon. [a] The corresponding unactivated 1,3-diene **2** was used instead of **2a**. [b] Nucleophile **S3o** (1.0 equiv.) was used, K_2CO_3 (1.5 equiv.) as base. [c] Sodium 4-toluensulfinate (1.0 equiv.) was used as nucleophile, K_2CO_3 (1.5 equiv.) as base.

2.3 Further applications of the radical interrupted Heck reaction/allylic substitution cascade.

Notably, two medicinally interesting drugs (*norquetiapine* and *desloratidine*) could be employed in this newly-developed, three-component method to generate complex tertiary amine products (**134** and **135**), which would be difficult to access using existing synthetic methodologies (**Scheme 5a**).[290]

Sequential palladium-catalyzed cross-coupling (interrupted Heck/allylic substitution, followed by Suzuki coupling) was also achieved (**Scheme 5b**). Again, the newly developed cascade provided a diverse way to build the intermediate **137**, which offers a route towards various medically interesting compounds (**Scheme 5c**).[3]

Scheme 5. Late-stage synthesis of complex drug-like tertiary amine product

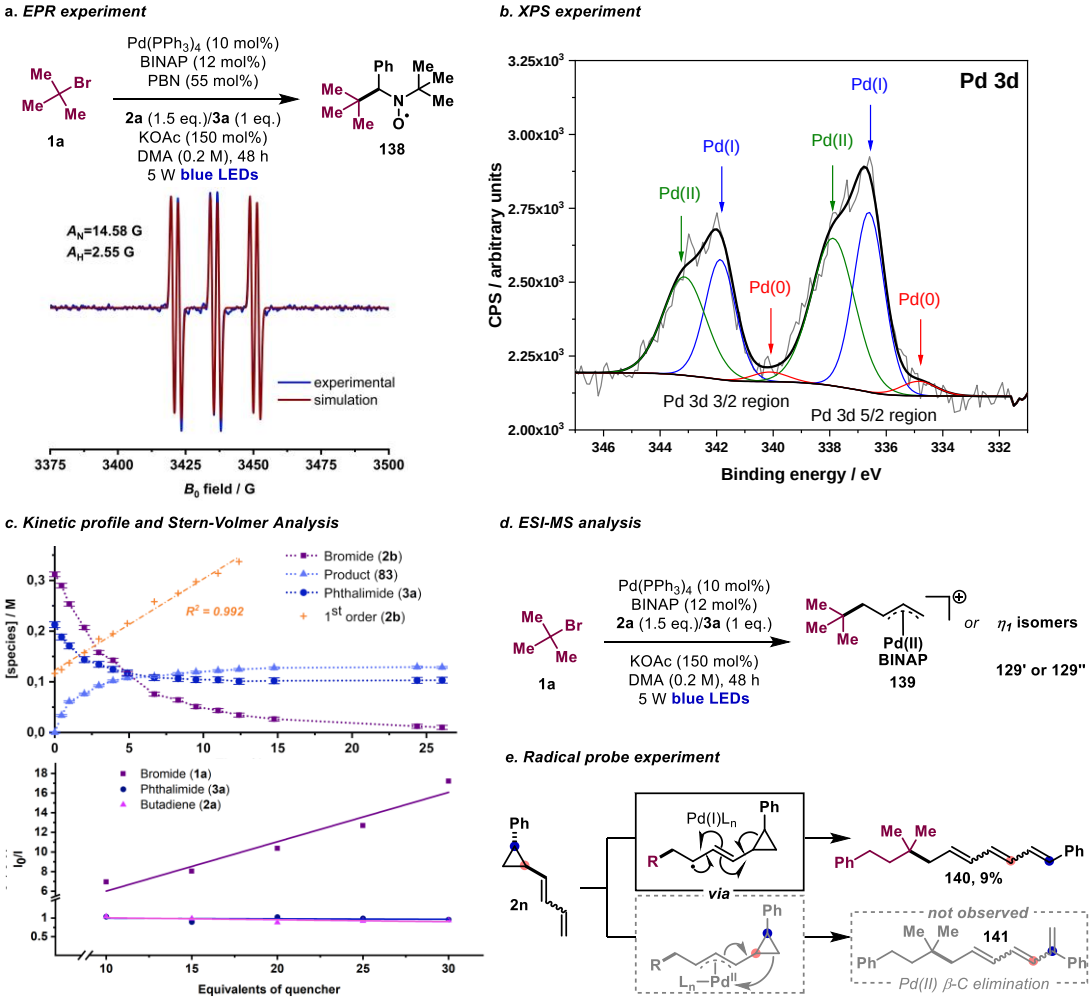


2.4 Preliminary mechanistic investigations

To shed light on the possible mechanism of this radical three-component coupling, the standard reaction was performed in the presence of the radical scavenger (TEMPO) and the desired product was not detected (see Supporting Information for further details). EPR experiments were also performed and the trapped intermediate **138** could be detected,[21l] indicating that the alkyl radical formation could only occur after irradiation with blue LEDs. This is in-line with previous results by Shang & Fu,[18a] Gevorgyan,[18c,21h-i] Rueping,[18h] Zhou[21v] and Yu[18i] that the formation of hybrid alkyl Pd(I) species **I** from alkyl bromides requires irradiation (**Fig. 6a**). X-ray photoelectron spectroscopy (XPS) measurement of the reaction mixture was carried out. The observed peak structures indicate the presence of three distinct oxidation states of Pd (**Fig. 6b**). These peaks can be attributed to Pd(II) (51.4 at.%), Pd(I) (44.4 at.%) and Pd(0) (4.2 at.%), which shows that the reaction may go through a Pd(0)–Pd(I)–Pd(II) mechanism. XPS peak fitting with only two components (i.e. Pd(II) and Pd(0)) would have required extraordinarily high full width at half maximum and very unusual peak shapes. Furthermore, it is known that oxidized Pd species may be reduced by X-ray exposure, which could be another reason for the presence of Pd(I) species. In this case, however, the influence of X-ray induced reduction can be discarded. Multiple measurements on the same position were carried out to show that the X-rays do not rapidly reduce the Pd species (**Fig. S5**) and the Pd(I) species must therefore stem from the reaction mixture. UV-vis experiments have shown that only palladium species absorb the visible light in the reac tion system[21l], thus reinforcing the hypothesis of the metal species acting as a photocatalyst. The kinetic profile of the reaction revealed that the consumption of the nucleophile **3a** follows 1st order kinetics. Interestingly, the cleavage of the bromide proceeded at a noticeably faster rate (**Fig. 6c**, up), hinting that *Tsuji-Trost* nucleophilic attack may be the rate-determining step of the overall catalytic manifold. Additionally, *Stern-Volmer* analysis proved that the palladium species could only be quenched by the alkyl bromide, consistent with previous results by Yu[18i] (**Fig. 6c**, down). Based upon these preliminary mechanistic results, we proposed that the hybrid alkyl Pd(I) species **I** could be generated *via* SET of a palladium(0) species to the alkyl bromide **1.** Delightfully, the allylpalladium complex (**139** or **139'** or **139''**) was detected by ESI-MS analysis (**Fig. 6d**), which indicated that the intermediate **I** could be trapped by 1,3-dienes to produce hybrid allylic Pd(I) radical **II**, which is capable of radical recombination to yield π-

allylpalladium complex **III**.[18h,21h,21l,24] Finally, nitrogen, oxygen, sulfur or carbon based nucleophiles could attack the intermediate **III** *via* allylic displacement[5] to generate the final three-component coupling product **4**. Meanwhile, the palladium catalyst is regenerated under redox-neutral conditions.[21g] Alternatively, hybrid alkyl Pd(I) radical species **I** may form a Pd(II)-alkyl intermediate *via* radical recombination; the same Pd(II) intermediate **III** could be formed through a carbopalladation step between 1,3-dienes and Pd(II)-alkyl intermediate. Radical probe experiments have indicated that radical addition to 1,3-dienes may happen. According to computational studies, using the radical allyl species to reduce either Pd(I) species or alkyl bromide as a means to initiate the catalytic cycle again, was shown to be thermodynamically unfeasible (+19.5 kcal/mol or +43.5 kcal/mol, respectively. See Supporting Information for detailed Information). When substituted 1,3-dienes were employed as coupling partners (**Scheme 4**), the observed initial attack at the unsubstituted position suggests that steric bulk plays a dominant role at this stage. While the regioselectivity control of allylic alkylation processes stems from manifold factors, there is consensus that steric encumbrance factors often play a major role in determining the site-selectivity of the nucleophilic attack.[5a-b, 31] Indeed, when sterically demanding groups (*e.g.* tertiary radicals) are attached to the diene *via* the first elemental step, the unsubstituted terminus of the π-allyl intermediate is comparatively more accessible than its decorated counterpart (see **129** in **Scheme 6**). In order to elucidate the role of the ligand, stoichiometric alkylation of preformed Pd(II)-allyl complexes revealed that catalytic systems featuring DPEPhos (β_n = 104°) and XantPhos (β_n = 108°)[32] afforded the allylated products with much lower regioselectivity for the terminal position (93:7 and 80:20, respectively) and decreased E/Z ratios (81:19 and 54:46, respectively), compared to BINAP (β_n = 93°, l:b 96:4, E/Z 86:14, see Supporting Information for details). These results are in agreement with previous findings from Van Leeuwen *et al.* and indicate that the ligand bite angle can influence the *syn:anti* ratio of the allyl intermediate, ultimately leading to a different product distribution.[33] Furthermore, such findings corroborate the pivotal role of the ligand not only during the SET event that yields the radical intermediate,[21l] but also in regioselectivity control of the *Tsuji-Trost* reaction.

Scheme 6. Preliminary mechanistic investigation



3. Conclusion

In summary, we have documented a general, modular three-component coupling, to achieve an interrupted radical Heck/allylic substitution cascade involving *unactivated* alkyl bromides for the first time. Nitrogen, oxygen, sulfur and carbon based nucleophiles could all be tolerated in this radical platform (>120 examples), sequential C(sp^3)–C(sp^3) and C–X bonds could be formed efficiently in excellent yields with excellent stereoselectivity under redox-neutral condition. Several complex synthetic architectures, such as ether, sulfone, and amine products were accessed via this unique, three-component coupling cascade for the first time. This synthetic methodology has also provided a diverse way to access intermediates of medicinally relevant drugs. We hope that this novel methodology will complement and expand the fields of transition-metal catalyzed cascades and radical cross-coupling reactions.

ASSOCIATED CONTENT

Materials and methods, detailed optimization studies, experimental procedures, mechanistic studies, EPR spectra and NMR spectra are available in the Supporting Information, which is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing interests.

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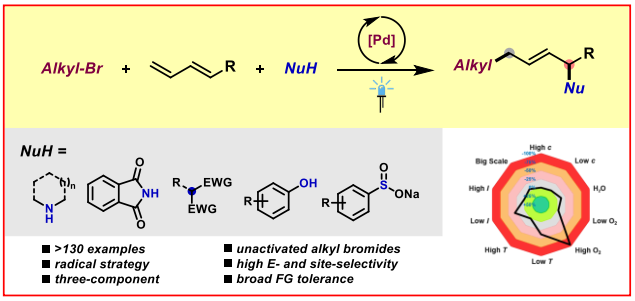
Alkyl-Br
R
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NuH =
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EWG
OH
ONa
>130 examples
radical strategy
three-component
unactivated alkyl bromides
high E- and site-selectivity
broad FG tolerance