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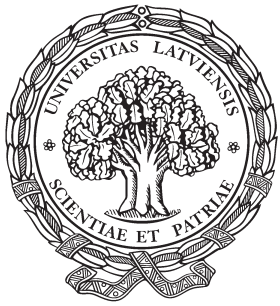

Igors Sokolovs

(HETERO)AROMĀTISKO SAVIENOJUMU C-H FUNKCIONALIZĒŠANA

PROMOCIJAS DARBS
Doktora grāda iegūšanai ķīmijas nozarē
Apakšnozare: organiskā ķīmija

Rīga, 2017

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ANOTĀCIJA

(Hetero)aromātisko savienojumu C-H funkcionalizēšana. Sokolovs I., zinātniskais vadītājs Dr. ķīm., prof. Sūna E. Promocijas darbs, 43 lappuse, 22 attēli, 24 literatūras avoti. Latviešu un Angļu valodā.

Darbā veikti nesimetrisko λ^3-jodānu un dažādu skābekļa un slāpekļa nukleofīlu mijiedarbības pētījumi. Balstoties uz iegūtajiem rezultātiem, sekmīgi izstrādātas viena reaktora secīgu daudzstadiju reakciju metodes C-H saites aktivēšanai/ funkcionalizēšanai. Metožu pielietojums ir parādīts uz plaša substrātu klāsta. C-H Saišu funkcionalizēšanas pieeja balstās uz *in situ* ģenerētu nesimetrisku λ^3-jodānu un dažādu nukleofīlu (acetātu, fenolātu, azīdu un plaša alifātisku un aromātisko amīnu) klāsta reakciju pārejas metālu (Pd, Cu) katalīzes apstākļos. Izstrādātas metodoloģijas pielietojums potenciālo zāļvielu "vēlīnai modificēšanai" parādīts antibakteriālā līdzekļa linezolīda sintēzē.

HETEROCIKLU FUNKCIONALIZĒŠANA, C-H SAITES AKTIVĒŠANA, PĀRĒJAS METĀLU KATALĪZE, λ^3-JODĀNI

SATURS

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IEVADS

Tēmas aktualitāte. Jaunu zāļvielu izstrāde saistīta ar ļoti plaša struktūranalogu klāsta sintēzi. Piemēram, veiksmīgai trāpījuma optimizācijai par līdersavienojumu (*hit-to-lead optimization*) parasti nepieciešams sintezēt milzīgu skaitu optimizējamā savienojuma struktūranalogu (bieži pat veselas savienojumu "bibliotēkas"). Tādēļ viens no mūsdienu organiskās sintēzes pamatuzdevumiem ir ērtu sintēzes metožu izstrāde struktūras-aktivitātes likumsakarību (SAR) pētījumiem medicīnas ķīmijā. Pēdējos gados zāļvielu molekulu dizainā plaši tiek izmantota t.s. "vēlīnās modificēšanas" (*late-stage modification*) pieeja, kura ļauj ievērojami paātrināt SAR pētījumus un racionalizēt sintētisko darbu. "Vēlīnās modificēšanas" pieeja paredz strukturālās daudzveidības ieviešanu pētāmajā bāzes struktūrā sintēzes beigu posmā, turklāt vēlamā aizvietotāja ievadīšanai optimizējamajā pamatstruktūrā nav nepieciešama tās iepriekšēja funkcionalizēšana. Konceptuāli vispiemērotākā sintēzes metodoloģija "vēlīnajai modificēšanai" ir C-H saišu funkcionalizēšanas pieeja. Diemžēl salīdzinoši lielais C-H saišu skaits caurmēra organiskajā molekulā neizbēgami izraisa reģioselektivitātes problēmas. Reģioselektivitātes nodrošināšanai C–H saišu funkcionalizēšanas reakcijās visbiežāk izmanto t.s. "virzošās grupas" – aizvietotājus, kuri nodrošina *orto-* vai *meta-*pozīcijās esošu C–H saišu aktivēšanu. "Virzošās grupas" pēc C-H funkcionalizēšanas ir jāaizvāc, un bieži tas nav triviāls uzdevums.

Darba mērķis. Promocijas darba pamatmērķis ir izstrādāt alternatīvu Csp2-H saišu funkcionalizēšanas metodoloģiju, kurā Csp2-H saišu aktivēšanas reģioselektivitāti noteiktu funkcionalizējamā savienojuma reaģētspēja elektrofīlās aromātiskās aizvietošanās apstākļos.

Darba uzdevumi.

1) Csp2-H Saišu funkcionalizēšanai izmantot hipervalentos joda(III) savienojumus;
2) Pārbaudīt hipotēzi par ligandu sametināšanas selektivitātes maiņu nesimetriskajos diaril-λ^3-jodānos pārejas metālu (Pd un Cu) katalīzes apstākļos;
3) Izstrādājamās sintēzes metodes balstīt uz "viena reaktora" secīgu daudzstadiju reakciju virkni.

Zinātniskā novitāte. Atradumam par ligandu sametināšanas selektivitātes maiņa nesimetriskajos diaril-λ^3-jodānos pārejas metālu (Pd un Cu) katalīzes apstākļos ir fundamentāla nozīme organiskajā ķīmijā. Jaunā teorētiskā atziņa ļāva izstrādāt jaunu sintēzes metodoloģiju paketi elektroniem bagātu (hetero)aromātisko savienojumu C-H funkcionalizēšanai, t.sk. C-H acetoksilēšanas reakciju veikšanai, diarilēteru sintēzei kā arī C-H azidēšanas un C-H aminēšanas reakciju veikšanai.

Darba praktiskā nozīme. Izstrādātā sintēzes metodoloģijas ir īpaši piemērota potenciālo zāļvielu "vēlīnajai" funkcionalizēšanai, un tāpēc darbam sagaidāms plašs pielietojums medicīnas ķīmijā. C-H Aminēšanas metodes piemērotība zāļvielu "vēlīnai" funkcionalizēšanai parādīta antibakteriālā līdzekļa *linezolīda* sintēzē.

PUBLIKĀCIJU SARAKSTS

Sintēzes metožu izstrāde un pielietojums ir pilnībā publicēti 5 zinātniskajos rakstos, tādēļ promocijas darbs noformēts kā publikāciju kopa:

1) Lubriks, D.; Sokolovs, I.; Suna, E. "Iodonium Salts Are Key Intermediates in Pd-Catalyzed Acetoxylation of Pyrroles" *Org. Lett.* **2011**, *13*, 4324-4327.

   I. Sokolovs izstrādāja 40% no eksperimentālā darba apjoma, noformēja pētījuma rezultātus atbilstoši žurnāla prasībām kā arī sniedza ieguldījumu publikācijas rakstīšanā.

2) Lubriks, D.; Sokolovs, I.; Suna, E. "Indirect C–H Azidation of Heterocycles via Copper-Catalyzed Regioselective Fragmentation of Unsymmetrical λ^3-Iodanes" *J. Am. Chem. Soc.* **2012**, *134*, 15436-15442.

   I. Sokolovs izstrādāja 40% no eksperimentālā darba apjoma, noformēja pētījuma rezultātus atbilstoši žurnāla prasībām kā arī sniedza ieguldījumu publikācijas rakstīšanā.

3) Sokolovs, I.; Lubriks, D.; Suna, E. "Copper-Catalyzed Intermolecular C-H Amination of (Hetero)arenes via Transient Unsymmetrical λ^3-Iodanes" *J. Am. Chem. Soc.* **2014**, *136*, 6920–6928.

   I. Sokolovs izstrādāja 70% no eksperimentālā darba apjoma, noformēja pētījuma rezultātus atbilstoši žurnāla prasībām kā arī sniedza ieguldījumu publikācijas rakstīšanā.

4) Berzina, B.; Sokolovs, I.; Suna, E. "Copper-Catalyzed para–Selective C–H Amination of Electron-Rich Arenes" *ACS Catalysis* **2015**, *5*, 7008–7014.

   I. Sokolovs izstrādāja 60% no eksperimentālā darba apjoma, noformēja pētījuma rezultātus atbilstoši žurnāla prasībām kā arī sniedza ieguldījumu publikācijas rakstīšanā.

5) Sokolovs, I.; Suna, E. "Para-Selective Cu–catalyzed C–H Aryloxylation of Electron-rich Arenes and Heteroarenes" *J. Org. Chem.* **2016**, 81, 371–379 (*Featured Article*).

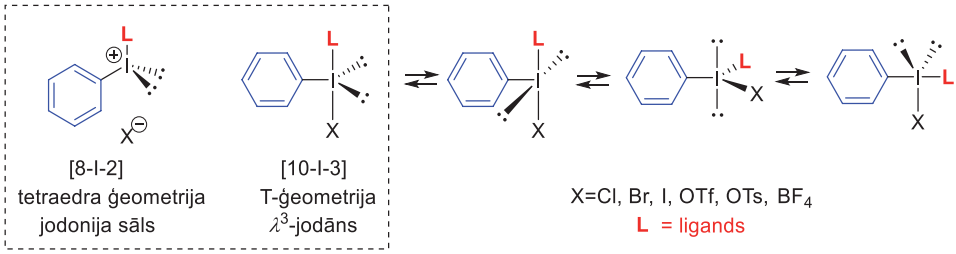
   I. Sokolovs izstrādāja 100% no eksperimentālā darba apjoma, noformēja pētījuma rezultātus atbilstoši žurnāla prasībām kā arī sniedza ieguldījumu publikācijas rakstīšanā.

1. NODAĻA.
PROMOCIJAS DARBA TĒMA UN PĒTĪJUMA KONCEPCIJAS IZKLĀSTS

1.1. Hipervalento joda(III) savienojumu uzbūve

Hipervalentos joda (III) savienojumus jeb λ^3-jodānus veido jods un trīs ligandi. λ^3-Jodāniem raksturīga T–veida ģeometrija (pseidotrigonālā bipiramīda), kuru nosaka divas atšķirīgas ķīmiskās saites jodānos. Ekvatoriāli novietoto ligandu un joda(III) atomu savieno kovalenta σ-saite, savukārt aksiālo stāvokļu ligandus un joda centru saista t.s. hipervalentā saite (1.1. att.). Šķīdumos λ^3–jodāni ir konfiguracionāli nestabili, jo aksiālie un ekvatoriālie ligandi stājas apmaiņas reakcijā, ko sauc par pseidorotāciju (*Berry pseudorotation*). Stabilākajai λ^3–jodānu konfigurācijai raksturīgs telpiski lielākā liganda novietojums stēriski vismazāk traucētajā ekvatoriālajā pozīcijā.

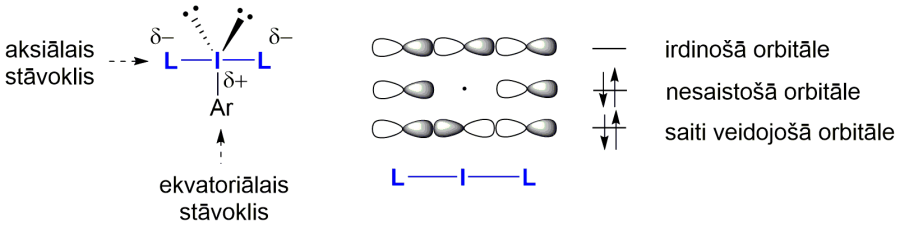
Saskaņā ar IUPAC rekomendācijām, hipervalentā joda(III) savienojumi jāsauc par λ^3-jodāniem. Plaši tiek izmantots diaril-λ^3-jodānu alternatīvais nosaukums "diariljodonija sāļi". Tas ir neprecīzs, jo "onija sāļiem" (piemēram, amonija un sulfonija sāļiem) raksturīga tetraedriska ģeometrija.[1] Hipervalento savienojumu raksturošanai bieži izmanto arī t.s. [N-X-L] nomenklatūru, kurā N ir elektronu skaits centrālā atoma X valences čaulā, bet L ir ligandu skaits, kuri saistīti ar centrālo atomu X. Attiecīgi λ^3-jodāni ir [10-I-3] konfigurācijas savienojumi, bet ariljodonija sāļi raksturojami kā [8-I-2] daļiņas (1.1. att.).



1.1. att. **λ^3-Jodāni.**

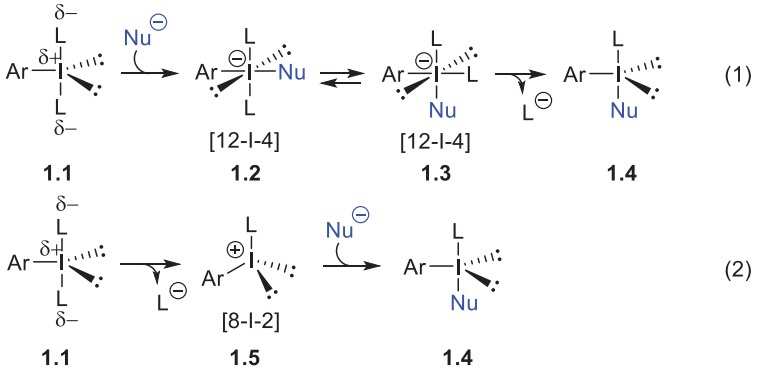
Hipervalentā saite joda(III) centru savieno ar diviem ligandiem, un to veido 2 elektroni no joda 5*p* orbitāles un pa vienam elektronam no katra liganda. Līdz ar to hipervalentajai saitei raksturīga 4 elektronu trīs centru konfigurācija, un to veido trīs lineāras molekulārās orbitāles: saiti veidojošā, nesaistošā un irdinošā (1.2. att.). Hipervalentajā saitē aizpildītas ir divas zemākās enerģijas orbitāles: saiti veidojošā un nesaistošā orbitāle. Joda(III) jonam piemīt gandrīz pilnu vienību liels pozitīvs daļlādiņš ($\sigma_I \approx +1$), bet uz pārējiem hipervalentās saites ligandiem ir negatīvs daļlādiņš. Joda(III) jona pozitīvais daļlādiņš nosaka aril-λ^3-jodanilaizvietotāja izteikti spēcīgo elektronakceptoro induktīvo efektu ($\sigma_I = 1.34$), kas ir salīdzināms ar diazonija sāļiem N_2^+–BF_4^- ($\sigma_I = 1.48$), un ir pat spēcīgāks nekā nitroaizvietotājam ($\sigma_I = 0.64$). Stipri polarizētā

hipervalentā saite nosaka viselektronegatīvāko ligandu novietojumu hipervalentajā saitē (aksiālajos stāvokļos). Parādīts, ka λ^3-jodānu stabilitāte labi korelē ar aksiālo stāvokļu ligandu Hammeta aizvietotāju indukcijas konstantēm. Elektronegatīvi ligandi (vājš *trans* efekts) labāk stabilizē negatīvo daļlādiņu hipervalentajā saitē, tādējādi stabilizējot λ^3-jodānu. Turpretim ar elektrondonorām īpašībām apveltītie ligandi (spēcīgs *trans* efekts) pavājina liganda-I(III) hipervalento saiti, un destabilizē λ^3-jodānu. Liganda *trans* efektu iespējams paredzēt, izmantojot aizvietotāju Hammeta σ konstantes.[2]



1.2. att. **Hipervalentās orbitāles λ^3–jodānos.**

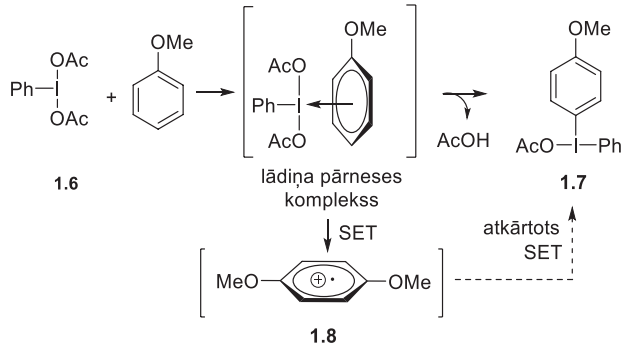
Šķīdumos λ^3-jodāni stājas ligandu apmaiņas reakcijā, kura var norisināties pēc asociatīvā vai disociatīvā mehānisma (1.3. att.). Asociatīvais mehānisms paredz ienākošā liganda (nukleofīla) uzbrukumu λ^3-jodāna **1.1** C-I saites irdinošajai σ* orbitālei, un *trans*-tetrakoordinēta jodāta **1.2** [12-I-4] veidošanos (1.3. att., vienādojums 1). *Trans*-jodāts **1.2** apgriezeniskajā reakcijā izomerizējas par *cis*-jodātu **1.3** un, disociējot heteroatoma ligandam L, veidojas jauns λ^3-jodāns **1.4**. Ligandu apmaiņa ir ātrs process. Par mazāk varbūtīgu tiek uzskatīts disociatīvais mehānisms, kurš ietver liganda sākotnēju disociāciju un jodonija [8-I-2] starpsavienojuma **1.5** veidošanos (1.3. att., vienādojums 2).



1.3. att. **Ligandu apmaiņa λ^3–jodānos.**

Līdztekus tādiem "klasiskajiem" nukleofīlajiem ligandiem kā acetāti, azīdi un fenolāti, par nukleofīlu reakcijā ar elektrofīlo aril-λ^3-jodānu **1.6** var kalpot arī elektroniem bagāta (hetero)aromātiska π-elektronu sistēma. Piemēram, anizols reaģē ar jodbenzola diacetātu ($PhI(OAc)_2$) **1.6** un veidojas diaril-λ^3-jodāns **1.7** (1.4. att.).

Visticamāk, jodāna **1.7** veidošanās notiek saskaņā ar elektrofīlās aromātiskās aizvietošanas S_EAr mehānismu (Frīdela-Kraftsa (*Friedel-Crafts*) reakcija). Diaril-λ^3-jodānu veidošanās padziļināti pētījumi ar elektronu paramagnētisko rezonanses metodi ļāva izvirzīt alternatīvu mehānismu, kas balstās uz sākotnēju katjonradikāļa **1.8** veidošanos viena elektrona pārnesē (*SET*) no elektroniem bagāta arēna uz elektrofīlo joda(III) centru (1.4. att.).[3]

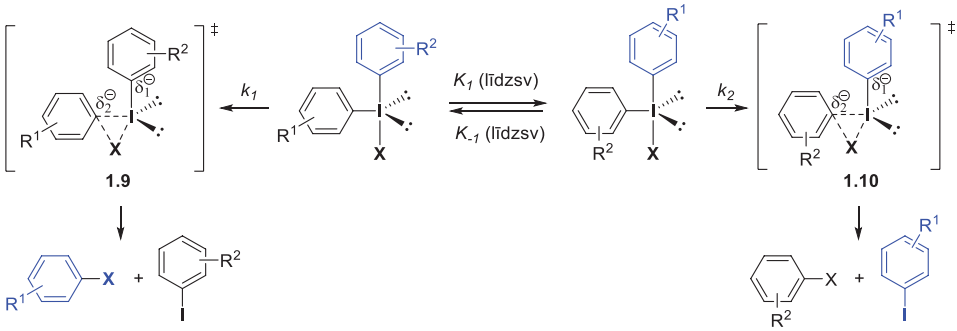


1.4. att. **Diaril-λ^3-jodānu veidošanās elektrofīlās aizvietošanās reakcijā.**

1.2. Reducējošā eliminēšanās diaril-λ^3-jodānos

Mūsdienu organiskajā sintēzē plaši izmantota diaril-λ^3-jodānu reakcija ir reducējošā eliminēšanās, kurā starp diviem diaril-λ^3-jodāna ligandiem veidojas saite, bet hipervalentais joda(III) centrs reducējas līdz jodīdam. Reducējošās eliminēšanas reakciju bieži dēvē par ligandu sametināšanas (*ligand coupling*) reakciju, un tās virzītājspēks ir okteta elektronu konfigurācijas ariljodīda veidošanās. Lai izceltu ariljodīda (ArI) izcilās aizejošās grupas īpašības (ArI ir ~ 10^6 reižu labāks nukleofūgs nekā trifluormetilsulfonāta anjons), ieviests termins "hipernukleofūgs".[1] Kvantu ķīmiskie aprēķini liecina, ka ligandu sametināšana diaril-λ^3-jodānos ir saskaņots process, kurā aksiālais ligands X uzbrūk ekvatoriāli novietotā arilliganda *ipso*-stāvoklim caur pārejas stāvokli **1.9** vai **1.10**.[4] Saskaņotais process nosaka, ka ligandu sametināšanas reakcijā var iesaistīties tikai ekvatoriālā stāvoklī novietotais ligands un hipervalentās saites (aksiālās pozīcijas) nukleofīlais ligands (1.5. att.). Jāatzīmē, ka ligandu sametināšanas jeb reducējošās eliminēšanas reakcijas pārejas stāvoklim ir augsta līdzība ar nukleofīlās aromātiskās aizvietošanas (S_NAr) reakcijas norisi.

Ņemot vērā relatīvi ātro ligandu apmaiņu (pseidorotāciju) diaril-λ^3-jodānos, ligandu sametināšanas reakcijā iesaistās līdzsvarā esoši diaril-λ^3-jodānu izomēri, un *nesimetrisko* diaril-λ^3-jodānu gadījumā ligandu sametināšanas reakcijā var veidoties divu produktu maisījums. Tomēr aktivācijas barjera ligandu apmaiņas reakcijai ir ievērojami zemāka nekā ligandu sametināšanas reakcijai ($K_1 >> k_1$ un k_2), un tāpēc ligandu sametināšanas selektivitāti *nesimetriskajos* diaril-λ^3-jodānos saskaņā ar Kurtina-Hammeta principu (*Curtin-Hammett principle*) nosaka reducējošās eliminēšanās reakcijas aktivācijas barjeru (jeb atbilstošo reakcijas ātruma konstanšu k_1 un k_2) atšķirība (sk. 1.5. att.).

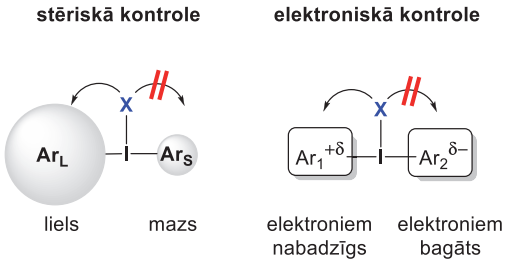


1.5. att. **Reducējošā eliminēšanās diaril–λ^3–jodānos.**

Ligandu sametināšanas selektivitāti *nesimetriskajos* diaril-λ^3-jodānos iespējams panākt, balstoties uz atšķirīgajām ligandu elektroniskajām un stēriskajām īpašībām. Kā liecina *ab initio* DFT kvantu ķīmiskie aprēķini, ligandu sametināšanas selektivitāti nosaka arilligandu *ipso*-oglekļa atomu elektrofilitāte jeb daļlādiņu δ_1^- un δ_2^- lielumi (1.5. att.). Attiecīgi ligandu sametināšanas reakcijā ar nukleofīlu stāsies arilligands ar mazāku negatīvo daļlādiņu jeb elektroniem nabadzīgākā aromātiskā sistēma.[5] Reaģētspējas atkarība no arilliganda elektrofilitātes (selektivitātes *elektroniskā kontrole*) akcentē diaril-λ^3-jodānu reducējošās eliminēšanās mehānisma līdzību ar nukleofīlās aromātiskās aizvietošanas (S_NAr) reakciju.

Ja viens no arilligandiem satur *orto*-aizvietotāju, ligandu sametināšanas selektivitātes elektroniskā kontrole vairs nav spēkā. Šādos nesimetriskajos diaril-λ^3-jodānos nukleofīlais ligands X veido saiti ar stēriski vairāk traucētu *orto*-aizvietoto ligandu neatkarīgi no arilligandu *ipso*-oglekļa atomu elektrofilitātes. Selektivitātes *stēriskās kontroles* (jeb t.s. "*orto-efekta*")[6] pamatā ir telpiski traucētā arilliganda tieksme atrasties nesimetriskā diaril-λ^3-jodāna ekvatoriālajā stāvoklī. Ekvatoriālais novietojums samazina telpisko mijiedarbību ar citiem ligandiem T-veida kompleksā un tāpēc termodinamiski ir visizdevīgākais.

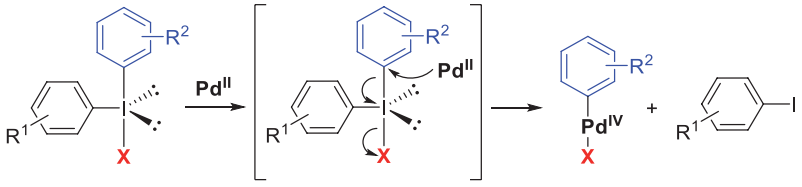
Diaril-λ^3-jodānu ligandu elektronisko un stērisko īpašību novērtēšana ļauj prognozēt selektivitāti ligandu sametināšanas reakcijā: hipervalentajā saitē novietotais nukleofīlais ligands X reaģēs vai nu ar stēriski vairāk traucētu (*orto*-aivietotu) arilligandu, vai ar elektroniem nabadzīgāko arilligandu (1.6. att.).



1.6. att. **Ligandu sametināšanas selektivitāte *nesimetriskajos* diaril-λ^3-jodānos.**

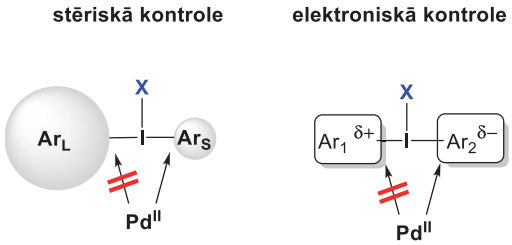
Orto-efekts bieži dominē pār stērisko kontroli. Līdz ar to nukleofīlā liganda X selektīvu reakciju ar telpiski mazāk traucētu un elektroniem bagātu ligandu parastajos apstākļos nodrošināt nav iespējams.

Diaril-λ^3-jodāniem raksturīga augsta reaģētspēja oksidējošās pievienošanās reakcijās ar pārejas metālu kompleksiem. Pateicoties joda (III) savienojumu izteiktajai elektrofilitātei un ariljodīdu lieliskajām aizejošās grupas (nukleofūga) īpašībām, diaril-λ^3-jodāni reaģē ne tikai ar Pd(0) metālorganiskajiem savienojumiem, bet arī spēj oksidēt mazāk reaģētspējīgus Pd(II) kompleksus par nestabilām Pd(IV) daļiņām[7] vai Pd(III)-Pd(III) dimēriem[8] (1.7. att.).



1.7. att. **Diaril-λ^3-jodānu oksidējošā pievienošanās Pd(II) daļiņām.**

Lieliskā diaril-λ^3-jodānu reaģētspēja ar Pd(II) kompleksiem ļāva izmantot hipervalentos joda(III) savienojumus kā reaģentus C-C saites sametināšanas reakcijā.[9,10] Svarīgi, ka *nesimetrisko* diaril-λ^3-jodānu oksidējošās pievienošanās reakcijā saiti ar pārejas metāliem (Pd un Cu) veido telpiski mazākais vai arī elektroniem bagātākais no arilligandiem,[11] turklāt ligandu pārneses selektivitātes noteikšanā stēriskie efekti dominē pār elektroniskajiem. Līdz ar to, pārejas metālu (Pd un Cu) klātbūtne pilnīgi izmaina *nesimetrisko* diaril-λ^3-jodānu reducējošās eliminēšanas reakcijas selektivitāti (salīdzināt 1.8. att. un 1.6. att.).

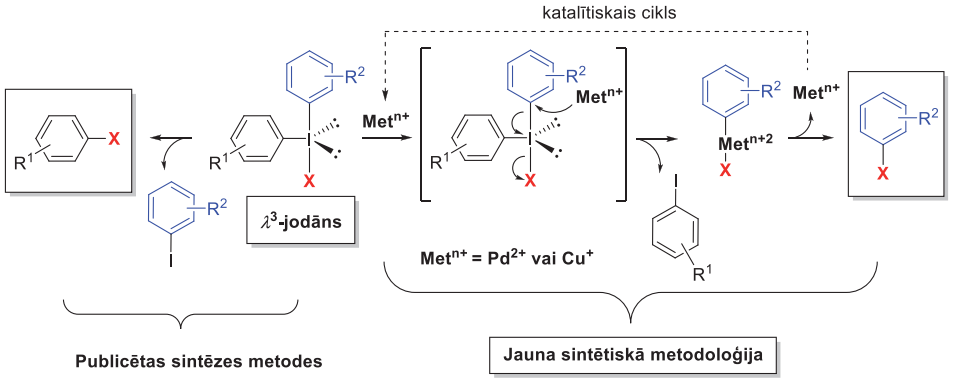


1.8. att. ***Nesimetrisko*** **diaril-λ^3-jodānu un Pd(II) reakcijas selektivitāte.**

Lai veicinātu vēlamā arilliganda selektīvu pārnesi no *nesimetriskā* diaril-λ^3-jodāna uz pārejas metālu kompleksiem, hipervalento joda(III) savienojumu dizainā bieži tiek izmantoti telpiski īpaši traucēti un tādēļ ar pārejas metāliem nereaģētspējīgi arilligandi (*dummy ligands*), piemēram, 1,3,5-trimetilfenil[12] vai 1,3,5-triizopropilfenil grupas.[13]

1.3. Promocijas darba pētījuma koncepcija

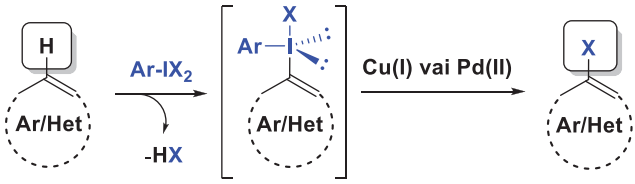
Promocijas darba uzsākšanas posmā veiktā literatūras analīze liecināja, ka pārejas metālu (Pd un Cu) reakcija ar *nesimetriskajiem* diaril-λ^3-jodāniem izmantota tikai C-C saites veidošanas reakcijās, turklāt pārejas metālu klātbūtne nodrošināja atšķirīgu ligandu pārneses selektivitāti, salīdzinot ar nekatalizētajām reakcijām. Tādēļ promocijas darbā tika izvirzīta hipotēze, ka **pārejas metālu (Pd un Cu) katalizatori var mainīt ligandu sametināšanas selektivitāti *nesimetriskajos* diaril-λ^3-jodānos, nodrošinot, ka hipervalentajā saitē novietotais nukleofīlais ligands X reaģēs vai nu ar stēriski *mazāk* traucētu vai ar elektroniem *bagātāko* no arilligandiem** (1.9. att.).



1.9. att. **Promocijas darba pamatkoncepcija**

Promocijas darba pirmais uzdevums bija pārbaudīt izvirzīto selektivitātes maiņas hipotēzi. Hipotēzes apstiprināšanās gadījumā tika plānots izstrādāt konceptuāli jaunu sintēzes metodoloģiju elektroniem relatīvi bagātu aromātisko un heteroaromātisko savienojumu C-H funkcionalizēšanai (1.10. att.). Sintēzes metodoloģijas izstrāde balstāma uz secīgu vairākstadiju "viena reaktora" (*one-pot*) procesu, kurš ietvertu:

1) *nesimetrisku* diaril-λ^3-jodānu *in situ* veidošanos elektroniem bagātu arēnu un heteroarēnu reakcijā ar piemērotu hiparvalento joda(III) reaģentu;
2) produktu veidojošo *selektīvu* reducējošo eliminēšanos diaril-λ^3-jodānos pārejas metālu (Pd, Cu) katalīzes apstākļos.

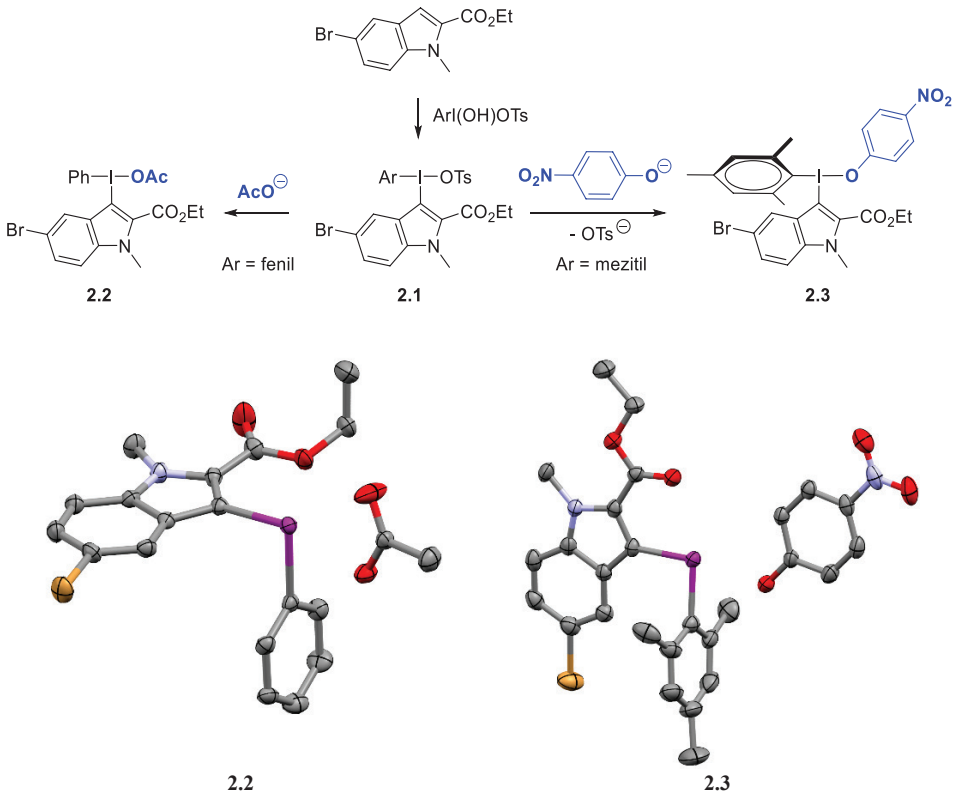


1.10. att. **Jaunas sintēzes metodoloģijas izstrāde**

2. NODAĻA.
PROMOCIJAS DARBA KONCEPCIJAS PĀRBAUDE UN PIELIETOJUMS

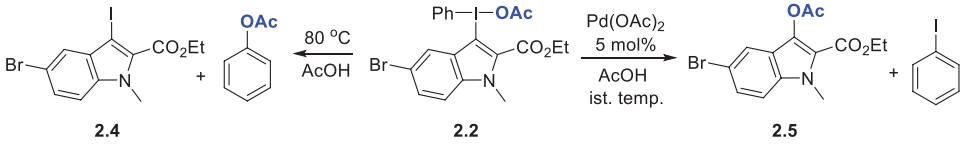
2.1. Ligandu sametināšanas selektivitāte diaril-λ^3-jodānos pārejas metālu katalīzes apstākļos

Promocijas darba pamatkoncepcijas pārbaudei tika izvēlēti skābekļa nukleofīlos ligandus (acetātu un fenolātu) saturošie *nesimetriskie* diaril-λ^3-jodāni **2.2** un **2.3**, kurus sintezējām ligandu apmaiņas reakcijā no hipervalentā joda(III) savienojuma **2.1**. Jāatzīmē, ka fenola ligandu saturošie diaril-λ^3-jodāni līdz šim nav bijuši sintezēti un izdalīti to zemās stabilitātes dēļ. λ^3-Jodāna **2.2** stabilitātes palielināšanai fenolāta ligandā ievadījām elektronus atvelkošo nitrogrupu, kura samazināja fenolāta liganda nukleofilitāti (*trans* efektu). Abu hiparvalento joda(III) savienojumu struktūras apstiprināšanai izmantota rentgenstruktūras analīzes metode (2.1. att.).



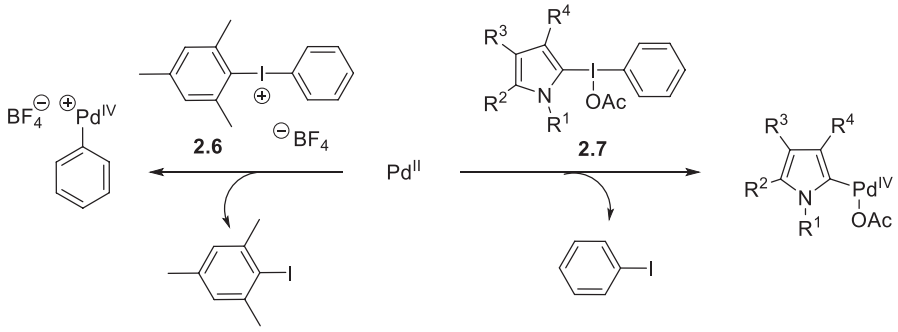
2.1. att. **Diaril-λ^3-jodānu 2.2 un 2.3 iegūšana un struktūra.**

Etiķskābes šķīdumā diaril-λ^3-jodāns **2.2** ir relatīvi stabils, bet 80 °C temperatūrā tas lēni sadalās par 3-jodindolu **2.4** un *O*-acilfenolu. Novērotā ligandu sametināšanas reaģētspēja (nukleofīlais acetāta ligands veido saiti ar elektroniem nabadzīgāko no diviem ligandiem) atbilst nekatalizētajai diaril-λ^3-jodānu reducējošās eliminēšanās norisei (sk. nodaļu 1.2). Katalītisku $Pd(OAc)_2$ daudzumu (5 mol%) klātbūtnē ligandu sametināšanas selektivitāte mainījās uz pretējo, un ar 81% iznākumu tika izdalīts acetoksiindols **2.5** (2.2. att.,). Etiķskābi aizstājot ar acetonitrilu, produkts **2.5** veidojās ar līdzīgu iznākumu (91%). Citi pārejas metālu sāļi, piemēram $PtCl_2$ (5 mol%) bija mazāk efektīvi katalizatori, bet, pievienojot 5 mol% $PtCl_4$ etiķskābē vai 10 mol% $Cu(OTf)_2$ dihlormetānā, reakcija nenotika. Lūisa skābju klātbūtnē reakcija vai nu nenotika (ar 4 ekvivalentiem $BF_3{\cdot}OEt$ dihlormetānā),[14] vai arī veidojās nesadalāms produktu maisījums (ar 2 ekvivalentiem TMS-OTf dihlormetānā).[15]



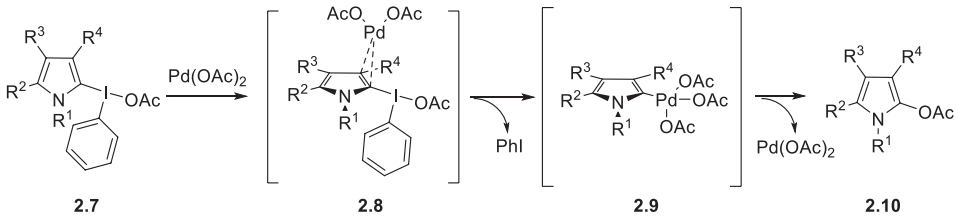
2.2 att. **Ligandu sametināšanas selektivitātes maiņa Pd(II) katalizatora klātbūtnē.**

Līdztekus indoliem $Pd(OAc)_2$ katalizētajā acetoksilēšanas reakcijā stājas arī aizvietoti piroli. Interesanti, ka pallādija katalīzes apstākļos nukleofīlais OAc ligands veido saiti ar stēriski vairāk traucētu *orto*-aizvietotu heterociklu (pirolu, indolu). Novērotā reģioselektivitāte ir negaidīta, jo *nesimetrisko* diaril-λ^3-jodānu gadījumā (piemēram, [Ar–I–Mes][BF_4] **2.6**) saiti ar pallādiju veido stēriski mazāk traucētā arilgrupa[16] (2.3. att.). Acīmredzot heteroaril(aril)-λ^3-jodānu **2.2** un **2.7** gadījumā acetoksilēšanas reģioselektivitāti kontrolē nevis stēriskie faktori, bet gan elektroniskie efekti: uz pallādija katalizatoru tiek pārnesta elektroniem bagātākā heteroarlilgrupa.[16]



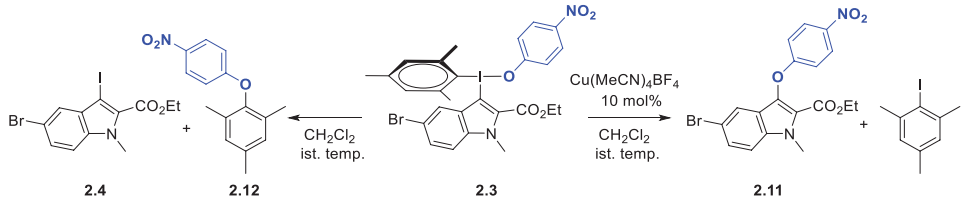
2.3. att. **Pd(II) katalizētās ligandu sametināšanas selektivitāte.**

Iespējams, ka pirola un indola gredzenu pārneses augsto selektivitāti nosaka sākotnēja Pd(II) η^2-koordinēšanās ar elektroniem bagātā piroliljodonija dubultsaites π-elektronu sistēmu (2.4. att. shēma, komplekss **2.8**),[17] kas arī nosaka tālākās oksidējošās pievienošanās selektivitāti un pirolil- Pd(IV) kompleksa **2.9** veidošanos.



2.4. att. **Pd(II) katalizētās ligandu sametināšanas selektivitātes iespējamais cēlonis.**

Pētījuma turpinājumā atrasts, ka ligandu sametināšanas reakciju *nesimetriskajos* diaril-λ^3-jodānos līdztekus pallādija sāļiem katalizē arī krieni lētāki un mazāk toksiski Cu(I) sāļi. Piemēram, $Cu(MeCN)_4BF_4$ komplekss reakcijā ar λ^3-jodānu **2.3** nodrošina selektīvu C-O saites veidošanos starp fenolāta ligandu un indola heterociklu (**2.11** : **2.4** = 5:1; sk. 2.5. att.). Ariloksiindola **2.11** veidošanās notiek maigos apstākļos (istabas temperatūrā) un salīdzinoši īsā laikā (30 min). Svarīgi, ka bez Cu(I) sāļu pievienošanas ligandu sametināšanas selektivitāte λ^3-jodānā **2.3** ir pretēja: CH_2Cl_2 šķīdumā I(III) savienojums **2.3** lēni pārvēršas par 3-jodindolu **2.4** un diarilēteri **2.12**. Nekatalizētā ligandu sametināšanās reakcija ir arī ievērojami lēnāka: pēc 3 h istabas temperatūrā izejvielas **2.3** konversija ir 25%, bet pilnu konversiju iespējams sasniegt tikai pēc 168 h (2.5. att.).



2.5 att. **Ligandu sametināšanas selektivitāte Cu(I) katalizētajā un nekatalizētajā reakcijā.**

Tika veikti arī kontroles eksperimenti, lai noskaidrotu diarilēteru sintēzē iesaistīto katalītiski aktīvo vara daļiņu oksidēšanas pakāpi. Pirmajā eksperimentā λ^3-jodāna **2.3** un $Cu(MeCN)_4BF_4$ katalizatora šķīdumam metilēnhlorīdā tika pievienots neokuproīns (2 ekv. attiecībā pret Cu(I) katalizatoru). Neokuproīns ir augsti specifisks Cu(I) jonus helatējošs aģents, kurš veido stabilu, oranžas krāsas kompleksu $CuI(neokuproīns)_2$.[18] Neokuproīna pievienošana ievērojami palēnināja λ^3-jodāna **2.3** konversiju, kas saniedza tikai 15% pēc 6 h, pretstatā 100% konversijai pēc 90 min Cu(I) katalizatora klātbūtnē. Turklāt neokuproīna klātbūtnē kā vienīgie produkti veidojās 3-jodindols **2.4** un ēteris **2.12**, bet ariloksiindols **2.11** reakcijas maisījumā netika novērots. Rezultāti apstiprina neokuproīna inhibējošo ietekmi uz Cu(I) katalizēto λ^3-jodāna **2.3** pārvēršanos par vēlamo produktu **2.11**. Neokuproīna klātbūtnē λ^3-jodāns **2.3** stājas nekatalizētajā ligandu sametināšanas reakcijā, un veidojas produkti **2.4** un **2.12**. Neokuproīna inhibējošais efekts liecina, ka katalītiski aktīvas ir Cu(I) daļiņas, un katalītiskajā ciklā notiek Cu(I)/Cu(III) oksidēšanās-reducēšanās pāreja. Iespējams, λ^3-jodāns **2.3** oksidējoši pievienojas Cu(I) daļiņām un veido Cu(III) starpproduktu. Katalītiskā cikla noslēguma

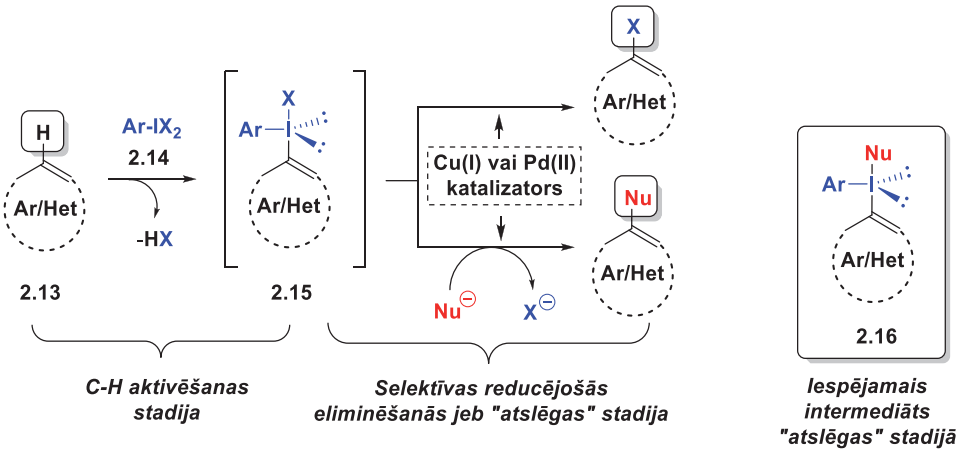
stadijā notiek reducējošā eliminēšanās ar diarilētera veidošanos un katalītiski aktīvo Cu(I) daļiņu reģenerēšanu.

Promocijas darbā veiktie pētījumi pilnībā apstiprināja promocijas darba pamathipotēzi par pārejas metālu (Pd un Cu) kompleksu spēju mainīt ligandu sametināšanas kemoselektivitāti *nesimetriskajos* diaril-λ^3-jodānos. Pārejas metālu katalizatoru spēja nodrošināt hipervalentajā saitē novietotā nukleofīlā liganda X reakciju ar elektroniem *bagātāko* no arilligandiem ļāva iztrādāt jaunu sintēzes metodoloģiju, kas īpaši piemērota zāļvielu molekulu "vēlīnajai" C-H funkcionalizēšanai.

2.2. Jaunu C-H funkcionalizēšanas metožu izstrāde

C-H Saišu funkcionalizēšanas metodoloģijas izstrādes koncepcija tika balstīta uz secīgu vairāku posmu "viena reaktora" (*one-pot*) procesu, kurš ietver:

1) **"C-H funkcionalizēšanas stadiju**" - nesimetrisko diaril-λ^3-jodānu **2.15** iegūšanu Frīdela-Kraftsa (*Friedel-Crafts*) reakcijā starp piemērotu hipervalento joda(III) reaģentu Ar-IX_2 **2.14** (X ir nukleofīlais ligands) un elektroniem relatīvi bagātiem aromātiskiem vai heteroaromātiskiem savienojumiem **2.13**;



2.6. att. **Vairākstadiju secīgas C-H funkcionalizēšanas metodes koncepcija.**

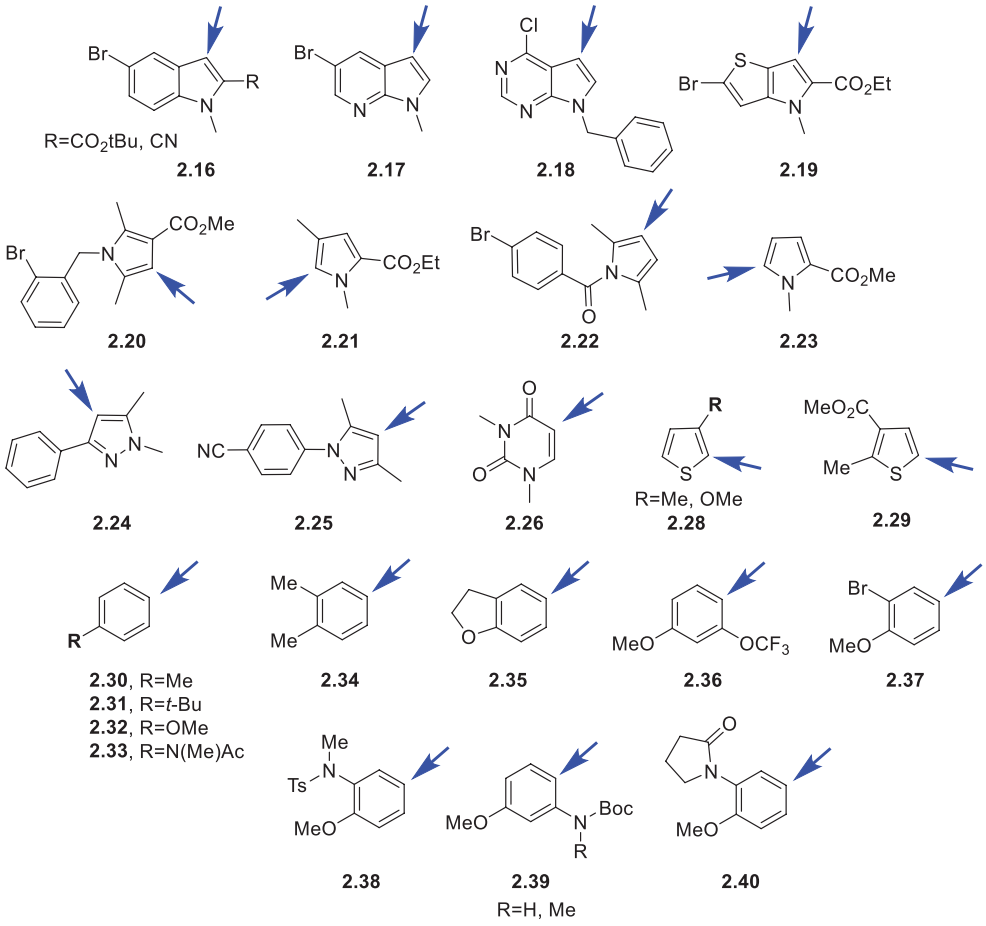
Vienkāršākajā variantā sintēzes metodoloģija paredz iegūt *vēlamo* nukleofīlo ligandu X saturošu *nesimetrisko* diaril-λ^3-jodānu **2.15** jau daudzstadiju procesa pirmajā posmā - C-H funkcionalizēšanas stadijā. Šim nolūkam izmantojami atbilstošie hipervalentie joda(III) reaģenti **2.14**. Diemžēl daudzu sintētiski nozīmīgu nukleofīlu X (piemēram, fenolu un azīdu) gadījumā atbilstošie λ^3-jodāna reaģenti **2.14** nav komerciāli pieejami un tie iepriekš jāsintezē. Turklāt amīnus saturoši λ^3-jodāna reaģenti **2.14** ir tik nestabili, ka tos pat nav iespējams iegūt. Tādēļ no metodoloģijas pielietojuma viedokļa ievērojami ērtākā ir alternatīva pieeja, kura paredz komerciāli pieejamu joda(III) reaģentu Ph-IX_2 (X=OAc, OTs) pielietošanu (hetero)aromātisko savienojumu

C-H funkcionalizēšanas stadijā un tai sekojošu nukleofīlo ligandu apmaiņas reakciju *nesimetriskajos* diaril-λ^3-jodānos **2.15** (2.6. att.).

2) **"ligandu apmaiņas stadiju"**, kurā notiek *vēlamā* nukleofīlā liganda (Nu=fenolāts, azīds) ievadīšana diaril-λ^3-jodāna starpsavienojumā **2.15**. Ligandu apmaiņas reakcija ir ātra, un tās rezultātā var veidoties jauns joda(III) starpsavienojums **2.16**. Ja par nukleofīlu tiek izmantots amīns (Nu=amīns), joda(III) starpsavienojums **2.16** visticamāk neveidojas zemās stabilitātes dēļ.
3) **"reducējošās eliminēšanās stadiju"** – pārejas metālu katalizēto saites veidošanos starp nesimetriskā diaril-λ^3-jodāna **2.14** hipervalentajā saitē novietoto nukleofīlo ligandu X un elektroniem *bagātāko* no arilligandiem (2.6. att.).

2.2.1. (Hetero)aromātisko savienojumu C-H funkcionalizēšanas stadija

C–H Funkcionalizēšanas stadijā no C–H neaizvietota (hetero)aromātiskā savienojuma tiek iegūts *nesimetriskais* diaril-λ^3-jodāns **2.15** (2.6. att.). Visi (hetero) aromātiskie savienojumi, kuri šķīdumā veido relatīvi stabilus diaril-λ^3-jodānus **2.15** (X=OAc, OTs) ir piemēroti substrāti C-H funkcionalizēšanas reakcijai. Joda(III) starpsavienojumu **2.15** veidošanās ātrums un iznākums atkarīgs no heteroaromātiskā savienojuma elektroniskajām īpašībām. Piemēram, elektroniem bagātie *N*-alkilpiroli **2.20**, **2.21** un **2.23** kā arī pirolo[2,3-*b*]piridīns **2.17** atbilstošos diaril-λ^3-jodānus veidoja jau 5 min laikā. Turpretim elektronus atvelkoša *N*-acilaizvietotāja ievadīšana pirolā (**2.22**) palēnināja reakciju līdz 30 min. Joda(III) starpsavienojumu **2.15** veidošanās no elektroniem mazāk bagātiem heterocikliem - indoliem **2.16**, pirolo[2,3-*d*]pirimidīna **2.18**, tieno-[3,2-*b*]pirola **2.19**, pirazoliem **2.24**, **2.25**, uracila **2.26** un tiofēniem **2.27**, **2.28** notika ievērojami lēnāk. Joda(III) starpsavienojumus **2.15** iespējams iegūt arī no elektroniem relatīvi bagātiem aromātiskajiem savienojumiem. Toluols **2.30** uzskatāms par reaģētspējas robežšķirtni: par toluolu elektroniem mazāk bagāti arēni ar Ar–IX_2 **2.14** nereaģē un atbilstošos *nesimetriskajos* diaril-λ^3-jodānus neveido. Pateicoties spēcīgākam aizvietotāja elektrondonorajam efektam, *terc*-butilbenzols **2.31** ir reaģētspējīgāks, nekā toluols (*terc*-Bu grupai $\sigma_p = -0.20$, bet metilgrupai $\sigma_p = -0.17$).[19]

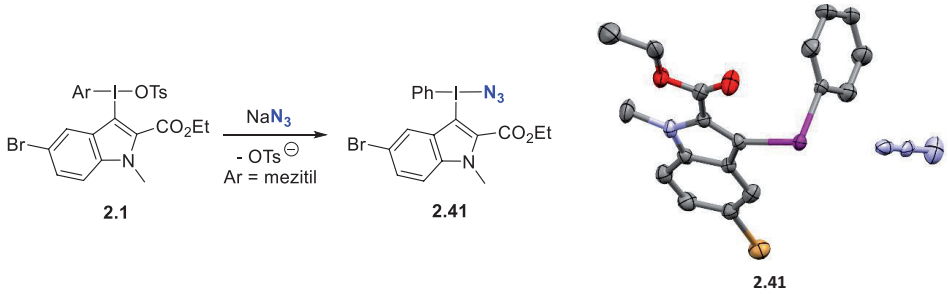


2.7. att. **C–H Funkcionalizēšanas reģioselektivitāte.**

Jodāna **2.15** veidošanās nosaka C-H funkcionalizēšanas reakcijas reģioselektivitāti. Lai gan reģioselektivitāte atkarīga no visu aizvietotāju elektronisko efektu kopuma, (hetero)aromātiskajos savienojumos tā atbilst elektrofīlās aromātiskas aizvietošanas jeb Frīdela-Kraftsa (*Friedel-Crafts*) reakcijai raksturīgajai selektivitātei. Attiecīgi indolos λ^3-jodāni veidojas β-pozīcijā, pirolos un tiofēnos – α-pozīcijā, bet pirazolos – 4. pozīcijā. 2,5-Diaizvietotu pirolu gadījumā atbilstošie jodonija sāļi tika iegūti β-pozīcijā bet uracils λ^3-jodānu veido 5. pozīcijā (2.7. att.). Aromātisko savienojumu gadījumā λ^3-jodāni selektīvi veidojas *para*-stāvoklī pret spēcīgāko elektrondonoro aizvietotāju, piemēram alkilgrupu (**2.30**, **2.31** un **2.34**) un alkoksigrupu (**2.32**, **2.35**). Aromātiskajos savienojumos, kuri satur vairākus mezomēros elektrondonoros aizvietotājus **2.36**–**2.40** un metoksigrupu, λ^3-jodāns veidosies *para*-stāvoklī pret metoksigrupu. Būtiski, ka C-H funkcionalizēšanai raksturīga augsta reģioselektivitāte, un izomēru veidošanās ar ^{1}H-KMR metodi netika novērota neviena substrāta gadījumā (2.7. att.).

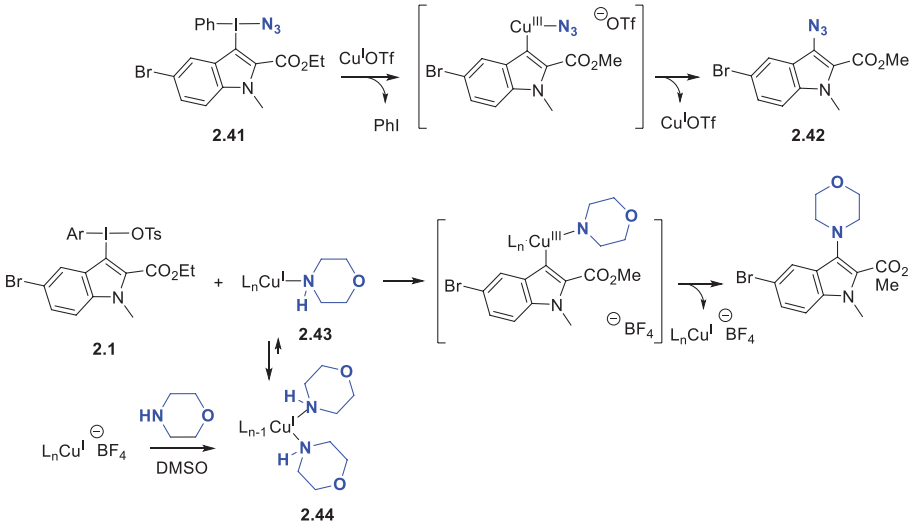
2.2.2. Ligandu apmaiņa diaril-λ^3-jodānu starpsavienojumos

C-H Funkcionalizēšanas stadijā izveidojies *nesimetriskais* diaril-λ^3-jodāns **2.15** stājas ligandu apmaiņas reakcijā ar ievadāmo nukleofīlu, veidojot jaunu joda(III) starpsavienojumu **2.16** (2.6. att.). Par nukleofīlu ligandu apmaiņas reakcijā izmantojot fenolātu vai azīdu, iespējams iegūt un izdalīt attiecīgos diaril-λ^3-jodānus (fenolāta gadījumā jodāns **2.3**, sk. 2.1. att.), kuru struktūra pierādīta ar rentgenstruktūras analīzes metodi (azīdu saturoša jodāna **2.41** gadījumā sk. 2.8. att.).



2.8. att. **Ligandu apmaiņa diaril-λ^3-jodānā 2.1**

C-H Azidēšanas reakcijas kinētikas pētījumi rāda, ka CuOTf-katalizētā jodāna **2.41** pārvēršanās par 3-azidoindolu **2.42** ir *pirmās* kārtas reakcija pret Cu(I) katalizatoru, un *nulltās* kārtas reakcija pret azīda jonu. Tātad Cu(I) ir iesaistīts katalītiskā cikla ātrumu limitējošajā stadijā, bet azīda pārnese joda(III) centra uz indola heterociklu ir iekšmolekulārs process. Viens no ticamākajiem C-H azidēšanas reakcijas mehānismiem ietver azido-jodāna **2.41** oksidējošo pievienošanos Cu(I) katalizatoram, un sekojošu azīda **2.42** reducējošo eliminēšanos (2.9 att.).

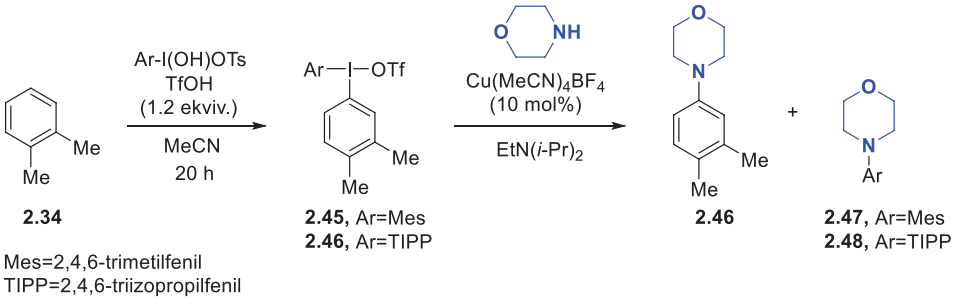


2.9. att. **C-H azidēšanas un aminēšanas iespējamie mehānismi.**

Reakcijā starp joda(III) starpsavienojumu **2.1** un amīnu nukleofīliem jaunu diaril-λ^3-jodānu veidošanos novērot neizdevās. Acīmredzot amīna ligandu saturoši joda(III) starpsavienojumi ir pārāk nestabili, lai tos varētu izdalīt un pierādīt struktūru. Iespējams, ka amīna ligandu saturoši diaril-λ^3-jodāni nemaz neveidojas, un C-N saites veidošanās notiek pēc cita mehānisma. Pēdējo pieņēmumu apstiprina reakcijas kinētikas pētījumi. Tie rāda, ka $(CuOTf)_2$-katalizētā diaril-λ^3-jodāna **2.1** (Ar=mezitil) C-H aminēšanas reakcija ar morfolīnu ir *pirmās kārtas* reakcija pret Cu(I) katalizatoru, *pirmās kārta* reakcija pret morfolīnu, un *nulltās kārtas* reakcija attiecībā pret jodānu **2.1**. Iegūtie rezultāti liecina, ka Cu(I) un morfolīns ir iesaistīti katalītiskā cikla ātruma limitējošajā stadijā, turpretim visas katalītiskā cikla stadijas ar jodāna **2.1** piedalīšanos ir ļoti ātras. Iespējams, ka Cu(I) katalizatora un morfolīna reakcijā veidojas vara(I)-amīna komplekss **2.43**, kurš ir līdzsvarā ar atbilstošo *bis*-amīna kompleksu **2.44**. Pieņemot, ka komplekss **2.44** ir katalizatora "depo forma" (*resting state*),[20] morfolīna disociācija līdzsvara apstākļos veido katalītiski aktīvo vara(I)-morfolīna kompleksu. Līdz ar to, iespējamais C-H aminēšanas mehānisms paredz, ka reakcijā ar jodānu **2.1** stājas nevis morfolīns, bet gan morfolīna-Cu(I) katalizatora komplekss (2.9. att.).

2.2.3. Ligandu sametināšanas selektivitāte reducējošā eliminēšanās stadijā

Lai panāktu augstu selektivitāti nukleofīlu (fenolātu, azīdu un amīnu) sametināšanās reakcijā ar (hetero)aromātiskajiem ligandiem, *nesimetrisko* diaril-λ^3-jodānu starpsavienojumu **2.15** (2.6. att.) iegūšanai tika izmantoti mezitilligandu saturoši joda(III) reaģenti **2.14** (Ar=mezitil; 2.6. att.). Mezitilgrupas pārnesi uz pārejas metāliem kavē telpiskie apgrūtinājumi, un tāpēc mezitilgrupu plaši izmanto kā "nereaģētspējīgu" ligandu (*dummy ligand*) hipervalento joda(III) savienojumu reakcijās ar pārejas metāliem. Diemžēl mezitilligandu izmantošana aromātisko savienojumu (piemēram, ksilola **2.34**) C-H aminēšanas reakcijās nodrošināja viduvēju selektivitāti (**2.46**:**2.47**=5:2; 2.10. att.).



2.34 **2.45,** Ar=Mes **2.46,** Ar=TIPP **2.46** **2.47,** Ar=Mes **2.48,** Ar=TIPP

Mes=2,4,6-trimetilfenil
TIPP=2,4,6-triizopropilfenil

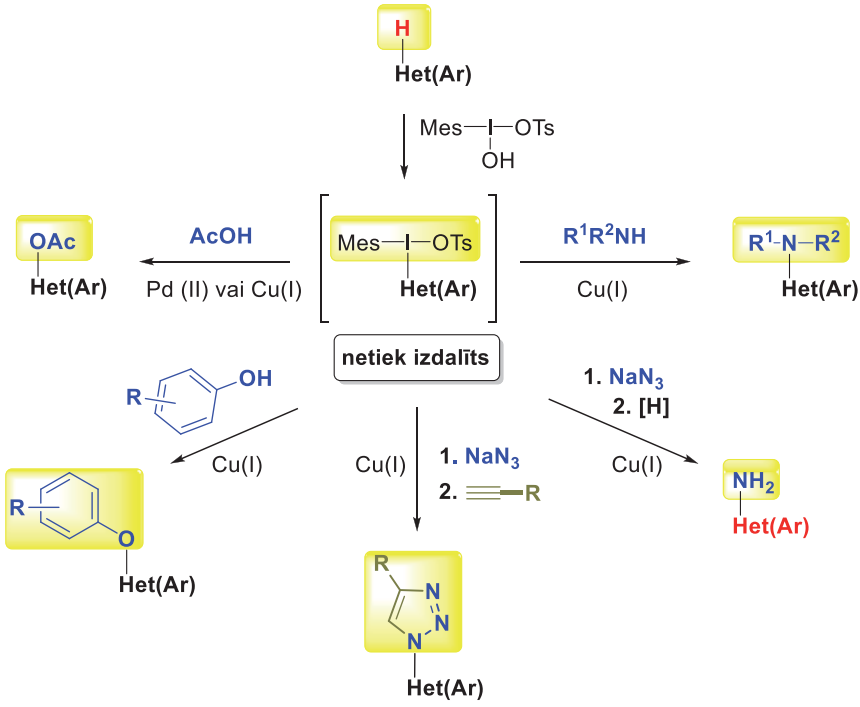
2.10. att. **C-H aminēšanas reģioselektivitāte atkarībā no liganda struktūras.**

Lai uzlabotu ligandu sametināšanās selektivitāti un tādējādi paaugstinātu vēlamā C-H aminēšanas produkta iznākumu, mezitilligandu vietā tika izmantoti telpiski vēl vairāk traucētu 1,3,5-triizopropilfenil-ligandu (TIPP) saturoši joda(III) reaģenti. TIPP Ligandus saturošu joda(III) reaģentu izmantošana ļāva būtiski paaugstināt ligandu

sametināšanas selektivitāti (**2.46**:**2.48**=98:2; 2.10. att.) un līdz ar to arī palielināt vēlamā produkta iznākumu.

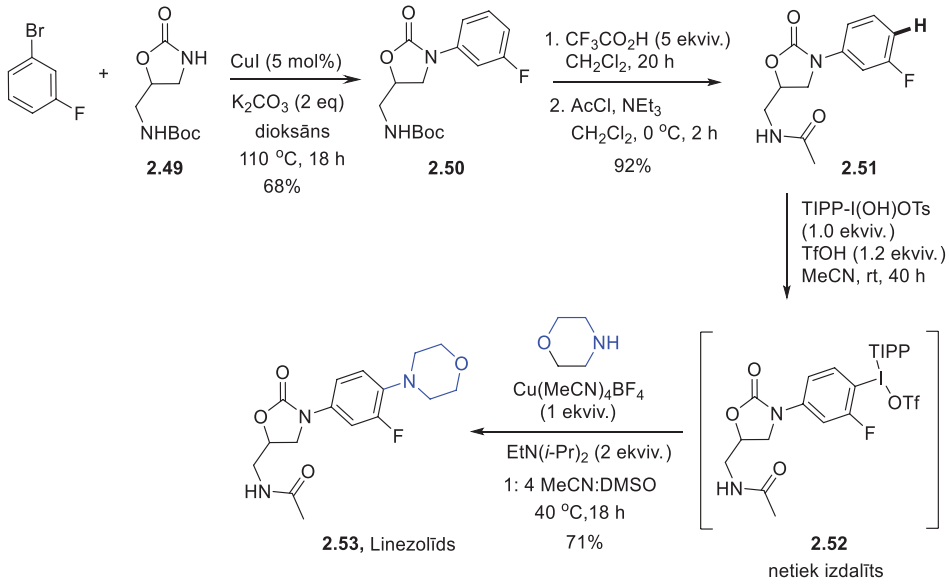
2.2.4. C-H Funkcionalizēšanas metodoloģijas pielietojuma klāsts un piemēri

Secīgā vairākstadiju "viena reaktora" (*one-pot*) C-H funkcionalizēšanas metodoloģija tika pielietota C-O un C-N saišu veidošanai elektroniem relatīvi bagātu heteroaromātiskajās un aromātiskajās sistēmās (2.11. att.). Vara(I)-katalizētās C-H azidēšanas reakcijas produkti – heteroaromātiskie azīdi izrādījās relatīvi nestabili, un to izdalīšana tīrā veidā bija apgrūtināta. Tādēļ iegūtie azīdi bez izdalīšanas tika tālāk reducēti līdz amīniem vai pārveidoti par 1,2,3-triazoliem vara(I) katalizētajā reakcijā ar acetilēniem.



2.11. att. **Izstrādāto C-H funkcionalizēšanas metožu klāsts.**

Izstrādāto C-H funkcionalizēšanas metodoloģijas piemērotība (hetero)aromātisko sistēmu vēlīnai funkcionalizēšanai parādīta antibiotikas Linezolīda (*linezolid*) sintēzē, kur morfolīna fragments aromātiskajā sistēmā ievadīts sintēzes noslēguma posmā (2.12. att.).



2.12. att. **Linezolīda (*linezolid*) sintēze.**

Antibiotikas sintēzes sākumposmā komerciāli pieejamais oksazolidinons **2.49** tika *N*-arilēts vara(I) katalizātora klātbūtnē. *N*-Boc Azsarggrupas nomaiņa savienojumā **2.50** pret *N*-acetil aizvietotāju ļāva iegūt C-H aminēšanas reakcijas izejvielu **2.51**. Nesimetriskā diaril-λ^3-jodāna **2.52** veidošanās reakcijai bija nepieciešams relatīvi ilgs laiks (40 h), lai sasniegtu pilnu konversiju. Morfolīna reakcijā ar joda(III) starpsavienojumu **2.52** bija nepieciešams stehiometrisks $Cu(MeCN)_4BF_4$ kompleksa daudzums. Linezolīds **2.53** tika izdalīts ar 71% iznākumu (2.12. att.). Jāuzver, ka izstrādātā linezolīda sintēzes metode ir lieliski piemērota plaša dažādu amīnu klāsta ievadīšanai linezolīda pamatstruktūrā **2.51** sintēzes noslēguma stadijā, un to iespējams izmantot linezolīda analogu bibliotēkas sintēzei.

SECINĀJUMI

1) Nesimetrisko diaril-λ^3-jodānu veidošanās notiek ar izcilu reģioselektivitāti, un tā atbilst elektrofīlas aromātiskas aizvietošanās reakcijai raksturīgajai selektivitātei. Aromātisko savienojumu gadījumā λ^3-jodāni selektīvi veidojas *para*-stāvoklī pret spēcīgāko elektrondonoro aizvietotāju;
2) Toluols iezīmē reaģētspējas robežšķirtni C-H funkcionalizēšanas reakcijā: par toluolu elektroniem mazāk bagāti arēni nereaģē ar hipervalentajiem joda(III) reaģentiem un atbilstošos *nesimetriskos* diaril-λ^3-jodānus neveido;
3) Pārejas metālu (Pd un Cu) katalizatori maina ligandu sametināšanas selektivitāti nesimetriskajos diaril-λ^3-jodānos, nodrošinot, ka hipervalentajā saitē novietotais nukleofīlais ligands reaģēs vai nu ar stēriski mazāk traucētu vai ar elektroniem bagātāko no arilligandiem. Vispiemērotākie katalizatori ir lēti un maztoksiski Cu(I) sāļi (CuOTf un $Cu(MeCN)_4BF_4$) kā arī $Pd(OAc)_2$;
4) Ligandu sametināšanas reakcijas selektivitāti iespējams uzlabot, palielinot nereaģētspējīgā arilliganda stēriskās prasības. Parejas metālu katalīzes apstākļos ligandu sametināšanas selektivitāte nesimetriskajos diaril-λ^3-jodānos pieaug sekojošā rindā

   fenil < **1,3,5-trimetilfenil** < **1,3,5-triizopropilfenil**;
5) Izstrādātā elektroniem bagātu (hetero)aromātisko savienojumu funkcionalizēšanas metodoloģija ir piemērota potenciālo zāļvielu bāzes struktūru "vēlīnajai modificēšanai". Par to liecina antibiotikas linezolīda "vēlīnās" C-H aminēšanas piemērs.

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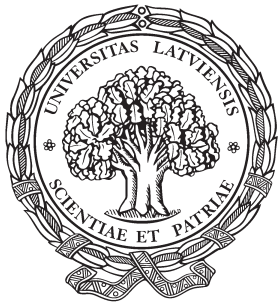

Igors Sokolovs

C-H FUNCTIONALIZATION OF (HETERO)ARENES

DOCTORAL THESIS
Submitted for the Degree of Doctor of Chemistry
Subfield of Organic Chemistry

Riga, 2017

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ABSTRACT

C-H Functionalization of (Hetero)arenes. Sokolovs I., supervisor Dr. chem., prof. Suna E. Doctoral thesis, 43 pages, 22 figures, 24 literature references. In Latvian and English.

Reactivity of unsymmetrical λ^3-iodanes with various *O*- and *N*-nucleophiles was investigated and new sequential one-pot multi-step C-H bond functionalization approach has been developed. The new methodology is based on a regioselective reaction of the *in situ* generated unsymmetrical λ^3-iodanes with a range of nucleophiles (acetates, phenolates, azides and various aliphatic and aromatic amines) in the presence of transition metal (Pd, Cu) catalysts. Suitability of the developed methodology for late-stage modification of the potential drug molecules was demonstrated in synthesis of antibacterial linezolid.

LATE-STAGE C-H FUNCTIONALISATION, C-H ACTIVATION, TRANSITION METAL CATALYSIS, λ^3-IODANES

INTRODUCTION

Importance of research topic. Development of new drug substances is associated with synthesis and screening of a broad scope of structural analogs. For instance, successful hit-to-lead optimization usually requires synthesis of considerable amount of structural analogs (often even focused compound libraries). Therefore, nowadays one of the main tasks in organic synthesis is development of convenient synthetic methods for structure-activity relationship (SAR) research in medicinal chemistry. In the last decades late-stage modification approach has become increasingly used in the design of drug-like compounds. The approach allows for significant acceleration of SAR studies and makes the synthetic work more rational. The late-stage modification approach is based on the introduction of structural variations into the lead structure in the final stage of the synthesis. Moreover, introduction of a desired substituent does not require its prior functionalization. Conceptually, the most suitable synthetic methodology for the late-stage modification is functionalization of C-H bonds. Unfortunately, relatively large number of C-H bonds in an organic molecule brings-up regioselectivity issues. To control the regioselectivity of the C-H bond functionalization, various directing groups are usually employed. Directing groups are substituents that activate *ortho*- or *meta*-C-H bonds. The directing groups must be removed after the C-H functionalization, which often is rather complicated task.

The main objective. The main objective of the Thesis work is the development of a complementary Csp2-H bond functionalization methodology, in which the regioselectivity of Csp2-H bond activation would be controlled by intrinsic reactivity of the modifiable compound in electrophilic aromatic substitution conditions.

Tasks of the Thesis research.

1) Use chemistry of hypervalent I(III) compounds for the development of Csp2-H bond functionalization methodology;
2) Verify the hypothesis about change of ligand coupling selectivity in unsymmetrical diaryl-λ^3-iodanes in the presence of transition metal (Pd and Cu) catalysts;
3) Employ one-pot sequential multi-step approach in the development of the synthetic methodology.

Scientific novelty. Finding that the presence of transition metal (Pd and Cu) catalysts brings about change of ligand coupling selectivity in unsymmetrical diaryl-λ^3-iodanes is of high importance in organic chemistry. This observation has allowed for the development of a set of new synthetic methodologies for C-H functionalization of relatively electron-rich (hetero)arenes, such as C-H acetoxylation and synthesis of diaryl ether as well as C-H azidation and C-H amination approaches.

Practical importance. The developed synthetic methodology is especially suitable for late-stage functionalization of drug-like compounds. As such, the synthetic method has potentially wide application in medicinal and pharmaceutical chemistry. Suitability of the developed C-H amination approach for late-stage functionalization has been demonstrated by synthesis of antibacterial *Linezolid*.

LIST OF PUBLICATIONS

C-H Functionalization methodology was used to form C-O and C-N bonds in relatively electron-rich heteroaromatic and aromatic systems.

This thesis is based on the following 5 papers:

1) Lubriks, D.; Sokolovs, I.; Suna, E. "Iodonium Salts Are Key Intermediates in Pd-Catalyzed Acetoxylation of Pyrroles" *Org. Lett.* **2011**, *13*, 4324-4327.

   I. Sokolovs contributed to development of concept and design of experiments; he carried out 40% of experimental work and contributed to drafting and critical review of the article.

2) Lubriks, D.; Sokolovs, I.; Suna, E. "Indirect C–H Azidation of Heterocycles via Copper-Catalyzed Regioselective Fragmentation of Unsymmetrical λ^3-Iodanes" *J. Am. Chem. Soc.* **2012**, *134*, 15436-15442.

   I. Sokolovs contributed to development of concept and design of experiments; he carried out 40% of experimental work and contributed to drafting and critical review of the article.

3) Sokolovs, I.; Lubriks, D.; Suna, E. "Copper-Catalyzed Intermolecular C-H Amination of (Hetero)arenes via Transient Unsymmetrical λ^3-Iodanes" *J. Am. Chem. Soc.* **2014**, *136*, 6920–6928.

   I. Sokolovs contributed to development of concept and design of experiments; he carried out 70% of experimental work and contributed to drafting and critical review of the article.

4) Berzina, B.; Sokolovs, I.; Suna, E. "Copper-Catalyzed para–Selective C–H Amination of Electron-Rich Arenes" *ACS Catalysis* **2015**, *5*, 7008–7014.

   I. Sokolovs contributed to development of concept and design of experiments; he carried out 60% of experimental work and contributed to drafting and critical review of the article.

5) Sokolovs, I.; Suna, E. "Para-Selective Cu–catalyzed C–H Aryloxylation of Electron-rich Arenes and Heteroarenes" *J. Org. Chem.* **2016**, 81, 371–379 (*Featured Article*).

   I. Sokolovs contributed to development of concept and design of experiments; he carried out 100% of experimental work and contributed to drafting and critical review of the article.

CHAPTER 1.
BACKGROUND OF THE DISSERTATION TOPIC AND THE RESEARCH CONCEPT

1.1. Structure of Hypervalent Iodine(III) Compounds

Hypervalent iodine(III) compounds or λ^3-iodanes consist of iodine and three ligands. λ^3-Iodanes have T-shaped (pseudo trigonal bipyramidal) geometry, which is determined by two different chemical bonds in iodanes. A ligand in an equatorial position is connected to iodine(III) atom by a covalent σ-bond, whereas the ligands at the axial positions are connected to the iodine center by so called hypervalent bond (Fig. 1.1.). λ^3–Iodanes are not stable in solutions because axial and equatorial ligands undergo an exchange reaction that is called pseudorotation (*Berry pseudorotation*). In a stable configuration of λ^3–iodanes sterically bulkier ligand is located in a less hindered equatorial position.

According to IUPAC recommendations, hypervalent iodine(III) compounds are to be named λ^3–iodanes. Often the term "diaryliodonium salts" is used instead of diaryl-λ^3-iodanes. However, it is not quite correct, because "onium salts" (e.g. ammonium or sulfonium) have tetrahedral geometry.[1] For description of hypervalent iodine compounds the so-called [N-X-L] nomenclature is often used, where N is the number of electrons in a valence shell of the atom X, and L is the number of ligands that are connected to the central atom X. Hence, λ^3–iodanes are compounds with [10-I-3] configuration, whereas ariliodonim salts are denoted as [8-I-2] species (Fig. 1.1).

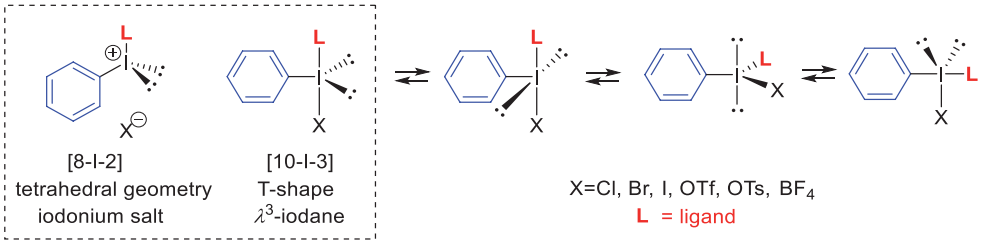

Figure 1.1. ***λ³-Iodanes.***

Iodine(III) center is connected to two ligands by a hypervalent bond, and it comprises 2 electrons from *5p* orbital of the iodine and one electron from each of the ligand. Thus, the hypervalent bond possesses four-electron three-center configuration, and it is formed of three linear molecular orbitals: bonding, nonbonding, and antibonding (Fig. 1.2.). Two orbitals with the lowest energy in the hypervalent bond are bonding and antibonding orbitals, and they are occupied. Central iodine(III) atom possesses full positive charge ($\sigma_I \approx +1$), whereas the other two ligands in a hypervalent

bond have partial negative charge. The positive charge of the iodine(III) ion determines the strong electron-accepting property of aryl-λ^3-iodonyl substituent (σ_I = 1.34) that is of comparable strength to that of diazonium salt N_2^+–BF_4^- (σ_I = 1.48), and is even stronger than that of a nitro substituent (σ_I = 0.64). Highly polarized hypervalent bond determines that the most electronegative ligands are positioned at both ends of the linear hypervalent bond (axial position). It has been shown what stability of λ^3-iodanes correlates with Hammett substituent constants of axial ligands. More electronegative ligands (low *trans* effect) better stabilize the negative partial charge in a hypervalent bond. However, electron donating ligands (strong *trans* effect) make hypervalent ligand-I(III) bond weaker, thus destabilizing λ^3-iodane. Magnitude of the *trans* effect of a ligand can be predicted by using Hammet σ constants.[2]

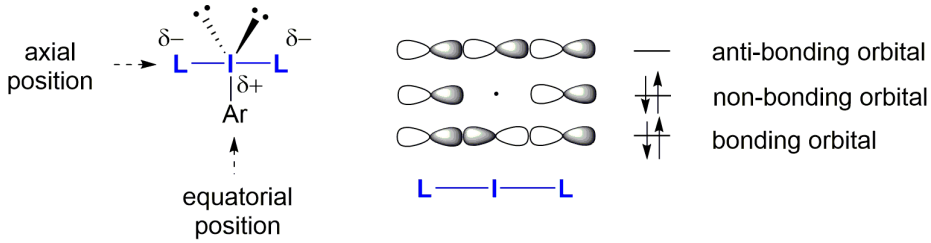

Figure 1.2. **Hypervalent orbitals in λ^3–iodanes.**

In solutions λ^3-iodanes undergo ligand exchange reaction, which can proceed via associative or dissociative mechanism (Fig. 1.3.). In an associative mechanism an incoming ligand (nucleophile) attacks the anti-bonding σ* orbital of C-I bond of λ^3-iodane **1.1**, and *trans*-tetracoordinated iodate **1.2** [12-I-4] is formed (Fig. 1.3.; equation 1). *Trans*-iodate **1.2** isomerizes in a reversible reaction to furnish *cis*-iodate **1.2**. After dissociation of heteroatom ligand L, a new λ^3-iodane **1.4** is formed. The ligand exchange process is fast. In a dissociative mechanism the ligand dissociates first to form iodonium [8-I-2] intermediate **1.5** (Fig. 1.3.; equation 2), however this process is considered to be a less likely scenario.

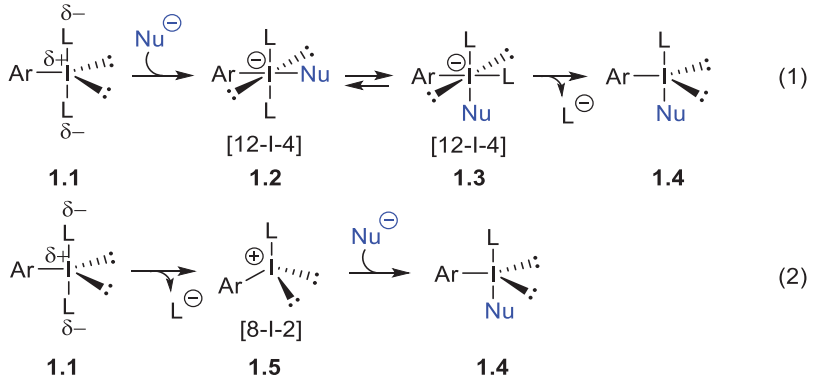

Figure 1.3. **Ligand exchange in λ^3–iodanes.**

The electron-rich (hetero)aromatic π-electron system can serve as a nucleophile in a reaction with electrophilic aryl-λ^3-iodane **1.6** in similarly to such "classical" nucleophiles as acetates, azides and phenolates. For instance, anisole reacts with iodobenzene diacetate ($PhI(OAc)_2$) **1.6** and diaryl -λ^3-iodane **1.7** is formed (Fig. 1.4.). Most likely that iodane **1.7** is formed according to the electrophilic aromatic substitution S_EAr mechanism (Friedel-Crafts reaction). More detailed studies using electron paramagnetic resonance (EPR) method resulted in a proposal of alternative mechanism for the formation of diaryl-λ^3-iodane. This involves an initial formation of radical cation **1.8** in one electron transfer (SET) step from electron-rich arene to the electrophilic iodine(III) center (Fig. 1.4.).[3]

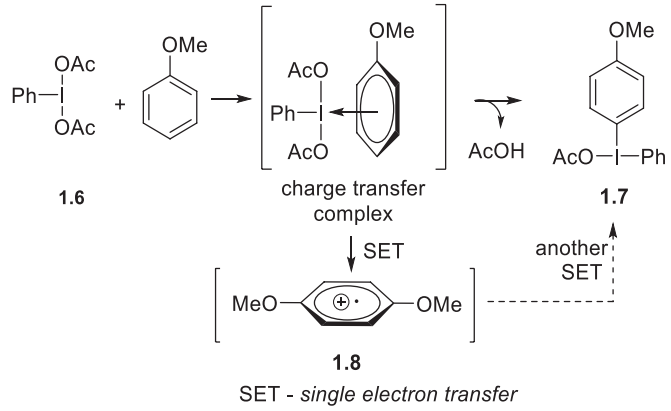

Figure 1.4. **Formation of diaryl- λ^3-iodanes in an electrophilic substitution reaction.**

1.2. Reductive Elimination in Diaryl-λ^3-iodanes

Reductive elimination from diaril-λ^3-iodanes is widely used nowadays to construct a new bond between two ligands of diaril-λ^3-iodane. Hypervalent iodine(III) species in this reaction is reduced to iodide. The reductive elimination reaction is often called a ligand coupling reaction, and the driving force of this reaction is the formation of aryliodide leaving group, which possesses octet electron configuration. A concept "hypernucleofuge" was introduced to emphasize excellent leaving group ability of aryliodide (ArI is ~ 10^6 times better nucleofuge than a trifluoromethylsulfonate anion).[1] *Ab initio* DFT calculations have shown that ligand coupling in diaril-λ^3-iodanes is a concerted process, where the axial ligand X attacks the *ipso*-position of the equatorial aryl ligand via the transition state **1.9** or **1.10**.[4] The concerted process determines that only the ligand in the equatorial position and the nucleophilic ligand of athe hypervalent bond (axial positions) can undergo the coupling reaction (Fig. 1.5.). It should be noted that, the transition state in a ligand coupling or reductive elimination reaction is very similar to that in a nucleophilic aromatic substitution reaction (S_NAr).

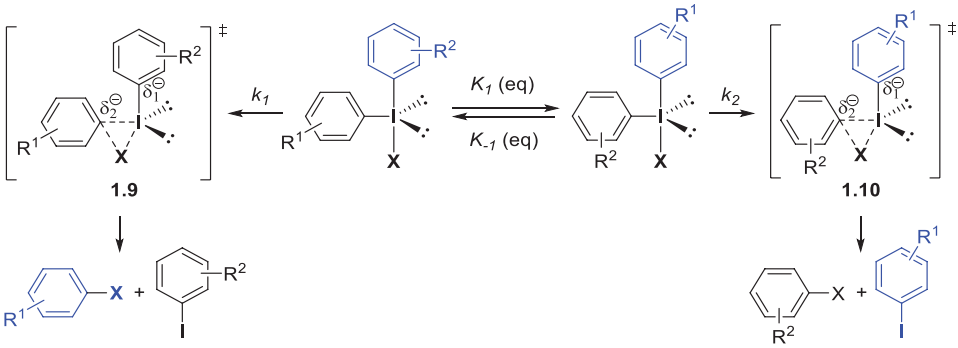

Figure 1.5. **Reductive elimination in diaril-λ^3-iodanes.**

Considering the relatively fast ligand exchange (pseudorotation) in diaryl- λ^3-iodanes, the ligand coupling reaction proceeds from the equilibrating diaryl-λ^3-iodane isomers. If *unsymmetrical* diaryl- λ^3-iodanes undergo a ligand coupling reaction, then a mixture of two products can be formed. However, activation energy of a ligand exchange reaction is significantly lower than that of the ligand coupling reaction ($K_1 >> k_1$ and k_2). Therefore selectivity in the ligand coupling reaction of unsymmetrical diaryl- λ^3-iodanes is defined by the difference between activation barriers of the reductive elimination reaction in accordance with the Curtin-Hammett principle (Fig. 1.5.).

The selectivity of the ligand coupling reaction in unsymmetrical diaryl-λ^3-iodanes can be achieved by exploiting the difference between electronic and steric properties of the ligands. *Ab initio* DFT calculations have shown that selectivity of the ligand coupling reaction is determined by electrophilicity of *ipso*-carbon atoms in the aryl ligand or by strength of the partial charges δ_1^- and δ_2^- (Fig. 1.5.). Thus, the aryl ligand with smaller negative partial charge (i.e. the most electron-poor aromatic system) will undergo the ligand coupling reaction with a nucleophile.[5] The reactivity dependence on electrophilicity of the aryl ligand (*electronic control* of selectivity) emphasize the similarity of reductive elimination mechanism in diaryl-λ^3-iodanes with that of the nucleophilic aromatic substitution (S_NAr) reaction.

If one of the aryl ligand contains an *ortho*-substituent, the ligand coupling selectivity is no longer controlled by the electronic factors. In these diaryl-λ^3-iodanes the nucleophilic ligand X forms a bond with a sterically more hindered *ortho*-substituted ligand regardless of electrophilicity of *ipso*-carbon atom in the aryl ligand. Steric control of the selectivity (or so called "*ortho*-effect")[6] is based on the preferred equatorial orientation of the sterically most hindered aryl ligand of unsymmetrical diaryl-λ^3-iodane. The equatorial orientation of the bulky *ortho*-substituted ligand helps to minimize steric interactions with the other ligand.

Evaluation of electronic and steric properties of diaril-λ^3-iodane ligands helps to predict selectivity in the ligand coupling reaction: the nucleophilic ligand X, which is located in a hypervalent bond, will react either with a sterically more hindered (*ortho*-substituted) aryl ligand, or with a more electron-poor aryl ligand (Fig. 1.6.).

The *ortho*-effect often dominates over steric control. Consequently, a selective reaction of a nucleophilic ligand X with a sterically less hindered and more electron-rich ligand apparently cannot be achieved.

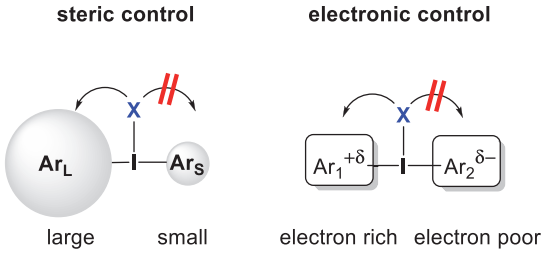

Figure 1.6. **Selectivity of ligand coupling in *unsymmetrical* diaryl-λ^3-iodanes.**

Diaryl-λ^3-iodanes show high reactivity in the oxidative addition reactions with transition metal complexes. Because of pronounced electrophilicity of iodine(III) compounds and excellent leaving group properties of aryl iodides diaryl-λ^3-iodanes not only react with Pd(0) organometallic compounds, but also they are capable to oxidize less reactive Pd(II) complexes to unstable Pd(IV) species[7] or Pd(III)-Pd(III) dimers[8] (Fig. 1.7.).

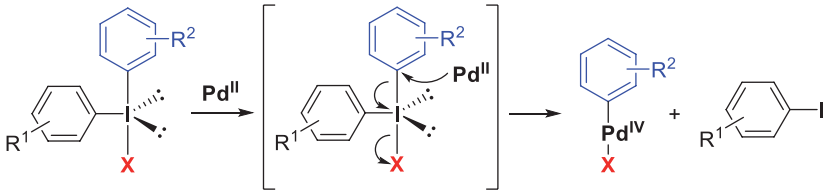

Figure 1.7. **Oxidative addition of diaryl-λ^3-iodanes to Pd(II) species.**

The excellent reactivity of diaryl-λ^3-iodanes with Pd(II) complexes has allowed the use of hypervalent iodine(III) compounds as reagents in C-C bond coupling reactions.[9,10] Noteworthy, in oxidative addition reactions of *unsymmetrical* diaryl-λ^3-iodanes, the bond is formed between a metal (Pd or Cu) and either sterically less hindered or more electron-rich aryl ligand.[11] Furthermore, steric effects dominate over the electronic ones in control of selectivity during the ligand transfer process. Thus, the presence of transition metals (Pd or Cu) completely changes the selectivity of reductive elimination reaction of unsymmetrical diaryl-λ^3-iodanes (compare Fig. 1.8. and Fig. 1.6.).

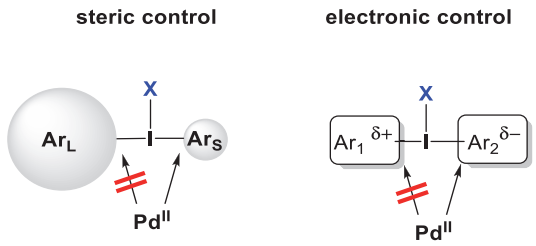

Figure 1.8. **Selectivity of a reaction between *unsymmetrical* diaryl-λ^3-iodanes and Pd(II).**

To favor a selective transfer of a desired aryl ligand from an *unsymmetrical* diaryl-λ^3-iodane to transition metal complexes, sterically very hindered dummy aryl ligands such as 1,3,5-trimethylphenil[12] or 1,3,5-triisopropilphenil groups are used in a design of hypervalent iodine(III) compounds.[13]

1.3. The Research Concept of the Doctoral Thesis.

Literature survey in the early stage of the Doctoral Thesis evidenced that reaction of transition metals (Pd and Cu) with *unsymmetrical* diaryl-λ^3-iodanes has been used only in C-C bond forming transformations. Furthermore, the presence of transition metals provided different selectivity in ligand transfer process as compared to noncatalyzed reactions. This has led to a hypothesis that **transition metal (Pd and Cu) catalysts can change the selectivity of ligand coupling in *unsymmetrical* diaryl- λ^3-iodanes by ensuring that in the hypervalent bond located nucleophilic ligand X will react either with a sterically less hindered or with a more electron-rich aryl ligand (Fig. 1.9.).**

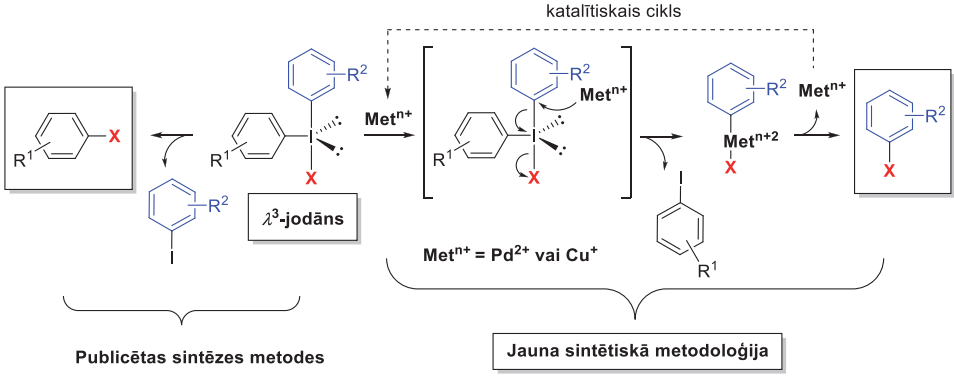

Figure 1.9. **The Research Concept of the Doctoral Thesis.**

The first task of the Thesis was to examine the selectivity change hypothesis. Confirmation of the hypothesis would make possible the development of a conceptually new synthetic methodology for C-H functionalization of relatively electron-rich aromatic and heteroaromatic compounds (Fig. 1.10.). Development of the synthetic methodology is to be based on the sequential multi-step one-pot process that would include:

1) *in situ* formation of *unsymmetrical* diaryl λ^3-iodanes in a reaction of electron-rich arenes and heteroarenes with a suitable hypervalent iodine(III) reagent;
2) transition metal (Pd, Cu) catalyzed *selective* reductive elimination of diaryl-λ^3-iodanes, which would furnish the desired products.

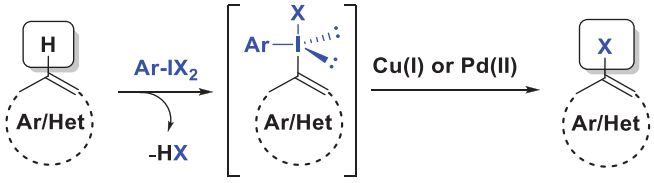

Figure 1.10. **Development of a new synthetic methodology.**

CHAPTER 2.
VERIFICATION OF THE HYPOTHESIS AND DEVELOPMENT OF NEW SYNTHETIC METHODOLOGY

2.1. Selectivity of the Transition Metal-Catalyzed Ligand Coupling in Diaryl λ^3-iodanes

To check the basic concept of the doctoral thesis, *unsymmetrical* diaryl-λ^3-iodanes **2.2** and **2.3** possessing oxygen-based nucleophilic ligands (acetate and phenolate) were chosen as substrates. These iodanes were synthesized from iodine(III) compounds by a ligand exchange reaction. It should be noted that phenol–containing diaryl-λ^3-iodanes have never been isolated in pure form because of their low stability. To decrease the nucleophilicity (*trans* effect) of phenol ligand and to increase stability of the λ^3-iodane **2.2**, an electron withdrawing nitro group was introduced in the phenolate ligand. Structures of the both iodine(III) compounds were confirmed by X-ray analysis (Fig. 2.1.).

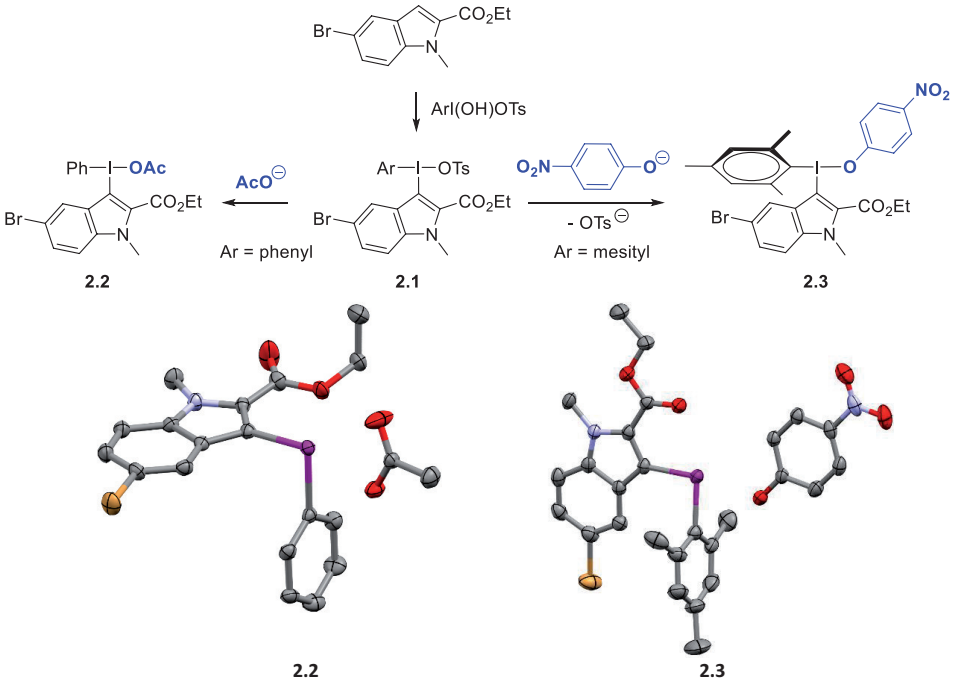

Figure 2.1. **Synthesis of diaril-λ^3-iodanes 2.2 and 2.3 and their structures.**

Diaril-λ^3-iodane **2.2** is relatively stable in a solution of acetic acid, however at 80 °C it undergoes slow decomposition to form 3-iodoindole **2.4** and *O*-acylphenol. The observed reactivity of the ligand coupling (the nucleophilic acetate ligand forms a bond with a more electron-deficient ligand) is consistent with noncatalyzed reductive elimination of diaryl-λ^3-iodanes (see Part 1.2). In the presence of catalytic amount of $Pd(OAc)_2$ (5 mol%) the selectivity of ligand coupling was changed to the opposite, and acetoxyindol **2.5** was isolated in 81% yield (Fig. 2.2.). Use of acetonitrile as solvent instead of acetic acid afforded product **2.5** in a similar yield (91%). Other transition metal salts, e.g., $PtCl_2$ (5 mol%), were less efficient as catalysts. In the presence of 5 mol% of $PtCl_4$ in acetic acid or 10 mol% of $Cu(OTf)_2$ in dichloromethane the reaction did not proceed at all. In the presence of Lewis acids the reaction either did not occurred (4 equivalents of BF_3·OEt in dichloromethane),[14] or a mixture of inseparable products was formed (2 equivalents of TMS-OTf in dichloromethane).[15]

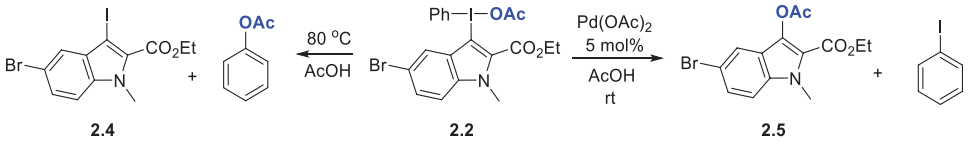

Figure 2.2. **Change of the ligand coupling selectivity in the presence of a Pd(II) catalyst.**

In addition to indoles, pyrroles can also undergo $Pd(OAc)_2$ catalyzed acetoxylation reaction. Interestingly, under palladium-catalyzed conditions the nucleophilic OAc ligand forms a bond with a sterically more hindered *ortho*-substituted heterocycle (pyrrole, indole). The observed regioselectivity is intriguing because it has been demonstrated that palladium catalyst forms the bond with a sterically less hindered aryl group of the *unsymmetrical* diaryl-λ^3-iodanes (e.g., [Ar-I-Mes][BF_4] **2.6**; see Fig. 2.3.).[16] Likely, in a case of heteroaryl(aryl)-λ^3-iodanes **2.2** and **2.7**, the regioselectivity is controlled by electronic factors rather than by steric ones: the more electron-rich heteroaryl group is transferred to the palladium catalyst.[16]

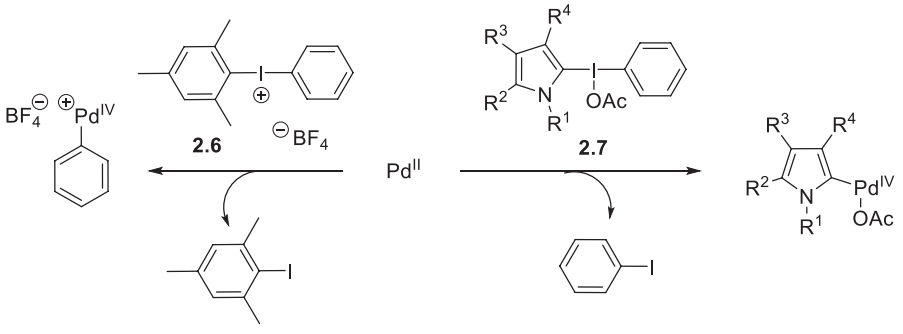

Figure 2.3. **Selectivity of the Pd(II) catalyzed ligand coupling reaction.**

It is also possible that the high selectivity of pyrrole and indole ring transfer is determined by initial Pd(II) η^2-coordination to the π-electron system of the electron-rich pyrrolidinium double bond (Fig. 2.4, complex **2.8**).[17] The η^2-coordination controls also the selectivity of the subsequent oxidative addition and formation of pyrrolyl-Pd(IV) complex **2.9**.

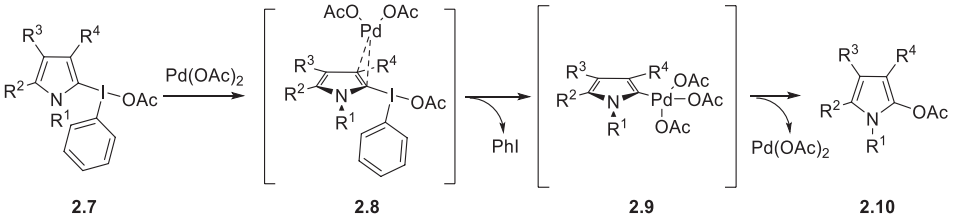

Figure 2.4. **Plausible mechanism of Pd(II) catalyzed ligand coupling reaction.**

Subsequently we have found that ligand coupling reactions of *unsymmetrical* diaryl-λ^3-iodanes can be catalyzed not only by palladium salts, but also by much cheaper and less toxic Cu(I) salts. For instance, selective formation of C-O bond between phenolate ligand and indole heterocycle was observed in a reaction of λ^3-iodane **2.3** with $Cu(MeCN)_4BF_4$ complex (**2.11**:**2.4** – 5:1, see Fig. 2.5.). Formation of aryloxyindole **2.11** proceeds under mild conditions (room temperature) and in a relatively short time (30 min). Importantly, selectivity of the ligand coupling in λ^3-iodane **2.3** is reversed in the absence of Cu(I) salts: in CH_2Cl_2 solution I(III) compound **2.3** is slowly transformed to 3-iodoindole **2.4** and diaryl ether **2.12**. Without a catalyst the ligand coupling reaction is much slower: the conversion of the starting material **2.3** is only 25% after 3 h at room temperature. Complete conversion can be achieved only in 168 h (Fig. 2.5.).

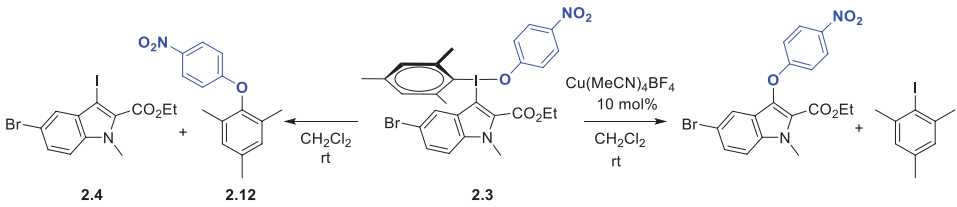

Figure 2.5. **Selectivity of the ligand coupling in a reaction with and without a Cu(I) catalyst.**

Control experiments were also performed to determine the oxidation state of the catalytically active copper species in the synthesis of diaryl ethers. In the first experiment neocuproine (2 equiv with respect to Cu(I) catalyst) was added to a solution of the λ^3-iodane **2.3** and $Cu(MeCN)_4BF_4$ catalyst in dichloromethane. Neocuproine is highly specific chelating agent for Cu(I) ions which forms stable, orange complexes $Cu^I(neocuproine)_2$.[18] Addition of neocuproine to the reaction significantly slowed down the conversion of λ^3-iodane. It reached only 15% in 6 h, as compared to 100% conversion in 90 min in the presence of Cu(I) catalyst. Furthermore, in the presence of

neocuproine 3-iodoindole **2.4** and ether **2.12** are the only products formed in the reaction, and aryloxyindole **2.11** is not observed. These results confirm, that neocuproine acts as an inhibitor in Cu(I)-catalyzed λ^3-iodane **2.3** conversion to the desired product **2.11**. λ^3-Iodane **2.3** undergoes a noncatalyzed ligand coupling reaction in the presence of neocuproine, and the products **2.4** and **2.12** are formed. The inhibitory effect of neocuproine suggests, that Cu(I) species are catalytically active, and Cu(I)/Cu(III) oxidation-reduction process occurs in the catalytic cycle. Likely, oxidative addition of λ^3-iodane to Cu(I) species occurs to furnish Cu(III) intermediate. Reductive elimination is the last step in the catalytic cycle, and diaryl ether is formed and catalytically active Cu(I) species are regenerated.

The obtained experimental evidence completely confirmed the key hypothesis of the doctoral Thesis that the chemoselectivity of the ligand coupling in diaryl-λ^3-iodanes can be altered in the presence of transition metal (Pd and Cu) catalysts. The ability of transition metal catalyst to control bond formation between nucleophilic ligand X and the most electron-rich of the two aryl ligands in *unsymmetrical* diaryl-λ^3-iodanes made possible the development of a new synthetic methodology that is especially suitable for the late stage C-H functionalization of drug-like compounds.

2.2. Development of C-H Functionalization Methods

The development of C-H bond functionalization methodology was based on a sequential multi-step one-pot process, which includes:

1) "**C-H functionalization step**" - synthesis of *unsymmetrical* diaryl-λ^3-iodane **2.15** in a Friedel-Crafts reaction between a suitable hypervalent iodine(III) reagent Ar-IX_2 **2.14** (X is a nucleophilic ligand) and relatively electron-rich aromatic or heteroaromatic compounds **2.13**;

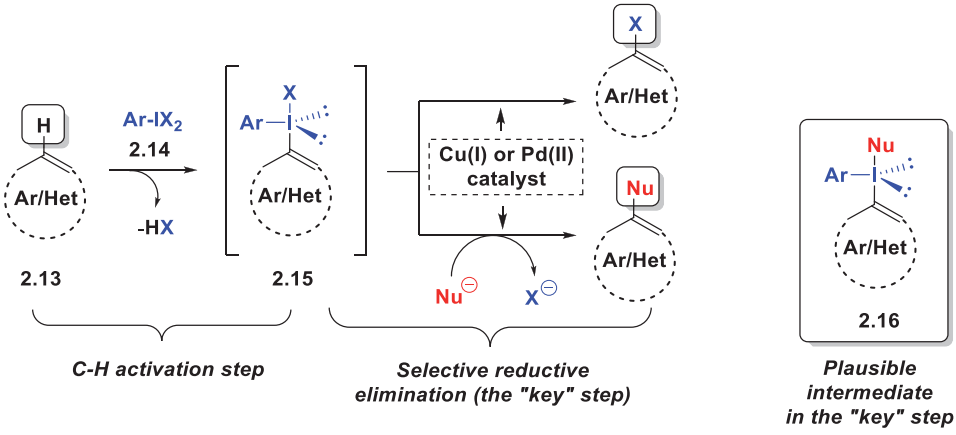

Figure 2.6. **The concept of a sequential multi-step C-H functionalization methodology.**

In the simplest version of a synthetic methodology, *unsymmetrical* diaryl-λ^3-iodane **2.15** possessing the *desired* nucleophilic ligand X is obtained already in the first stage of the multi-step process (C-H functionalization stage). For this purpose an appropriate hypervalent iodine(III) reagent **2.14** is to be used. Unfortunately, in the most cases λ^3-iodanes possessing a synthetically useful nucleophilic ligand X (such as phenol and azide) **2.14** are not commercially available and have to be synthesized beforehand. Furthermore, λ^3-iodanes containing certain X ligands such as amines are too unstable, so it is not possible to isolate them. Therefore, an alternative approach has been designed. Accordingly, commercially available iodine(III) reagents Ph-IX_2 (X=OAc, OTs) are used in the C-H functionalization step of (hetero)aromatic compounds to generate *unsymmetrical* diaryl-λ^3-iodanes. The *desired* nucleophilic ligand X is subsequently introduced by a ligand exchange reaction in **2.15** (Fig. 2.6.).

2) "**ligand exchange step**", where the *desired* nucleophilic ligand (Nu=phenolate, azide) is introduced into the diaryl-λ^3-iodane intermediate **2.15**. The ligand exchange reaction is fast, and it results in the formation ofa new iodine(III) intermediate **2.16**. However, if amine is used as a nucleophile (Nu=amine), the corresponding iodine(III) intermediate **2.16** likely is not formed due to its low stability.
3) "**reductive elimination step**" – transition metal catalyzed bond formation between the nucleophilic ligand X (located in a hypervalent bond of the *unsymmetrical* diaril-λ^3-iodane **2.14**) and *the most* electron-rich of aryl ligands (Fig. 2.6.).

2.2.1. C-H Functionalization Step of (Hetero)aromatic Compounds

In a C-H functionalization step the *unsymmetrical* diaryl-λ^3-iodane **2.15** is formed from a C-H unsubstituted (hetero)aromatic compound (Fig. 2.6.). All hetero(aromatic) compounds that can form relatively stable diaryl-λ^3-iodanes **2.15** (X=OAc, OTs) are suitable as substrates for the C-H functionalization reaction. The formation rate of iodine(III) intermediates **2.15** and their yields depend on electronic properties of the heteroaromatic compound. For instance, the corresponding diaryl-λ^3-iodanes were formed from electron-rich *N*-alkylpyrroles **2.20**, **2.21** and **2.23** as well as from pyrrolo[2,3-*b*]pyridine **2.17** in only 5 minutes. Introduction of electron-withdrawing *N*-acyl substituent into pyrrole (**2.22**) slowed down the reaction to 30 min. Formation of iodine(III) intermediated **2.15** from less electron-rich heterocycles – indoles **2.16,** pyrrolo[2,3-*d*]pyrimidine **2.18**, thieno-[3,2-*b*]pyrrole **2.19**, pyrazoles **2.24**, **2.25**, uracil **2.26** un thiophenes **2.27**, **2.28** occurred significantly slower. Iodine(III) intermediated **2.15** can be obtained also from relatively electron-rich aromatic compounds. Toluene **2.30** represents a borderline of reactivity: arenes that are less electron-rich than toluene do not react with Ar-IX_2 **2.14** and the corresponding *unsymmetrical* diaryl-λ^3-iodanes are not formed. Due to a strong electron-donating effect of the substituent, *tert*-butyl benzene **2.31** is more reactive than toluene (for *tert*-Bu group $\sigma_p = -0.20$, but for methyl group $\sigma_p = -0.17$).[19]

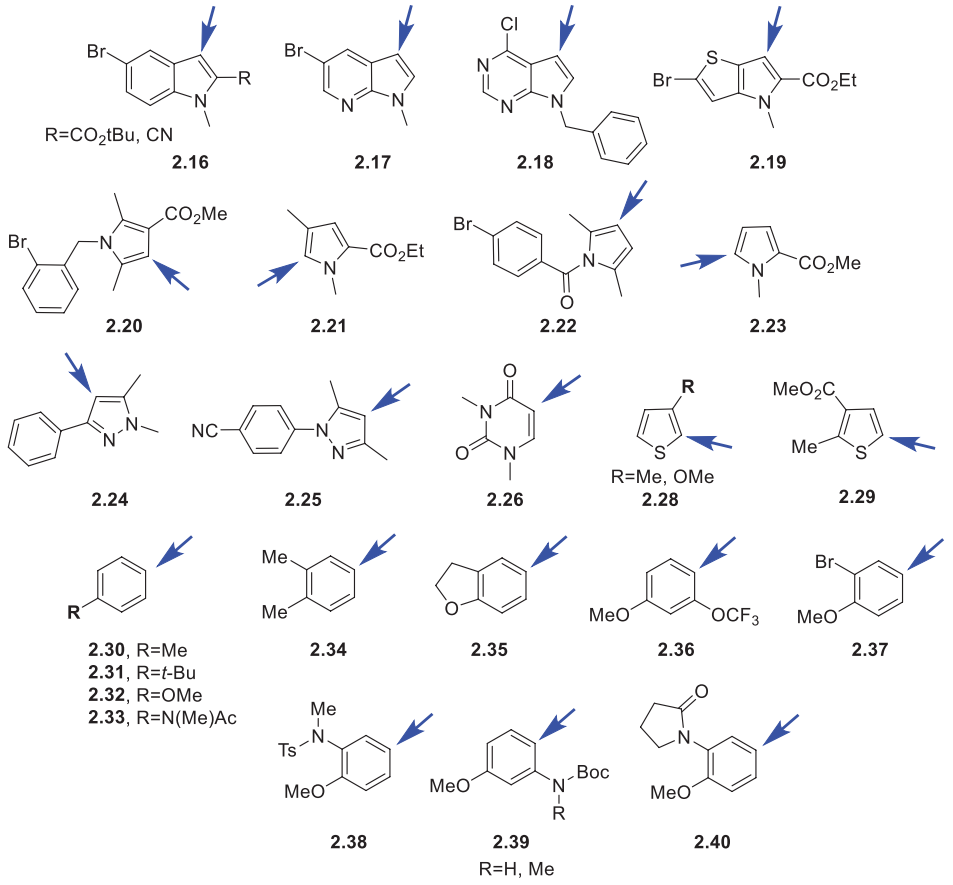

Figure 2.7. **Regioselectivity of the C-H functionalization step.**

The regioselectivity of the C-H functionalization reaction is determined at the step of iodane **2.15** formation. Although the regioselectivity is a result of the combined directing effects of substituents in heterocycles and arenes, in general, it is consistent with that of electrophilic aromatic substitution (S_EAr) reactions. Thus, λ^3-iodanes are formed at the β-position of indoles, at the α-position of pyrroles and thiophenes and at position 4 of pyrazoles. In the case of 2,5-disubstituted pyrroles the corresponding iodonium salts were formed at β-position, but uracil formed λ^3-iodane at the position 5 (Fig. 2.7.). In the case of aromatic compounds, λ^3-iodanes were selectively formed at the *para*-position to the strongest electron-donating substituent, for example, alkyl group (**2.30**, **2.31** and **2.34**) and alkoxy group (**2.32**, **2.35**). λ^3-Iodane is formed at the *para*-position to methoxy group in aromatic compounds that in addition to the methoxy group contain several more mesomeric electron-donating substituents **2.36**–**2.40**. Importantly, the C-H functionalization is highly regioselective, and the formation of regioisomers has never been observed by ^{1}H-NMR analysis (Fig. 2.7.).

2.2.2. Ligand Exchange in Diaryl-λ^3-iodane Intermediates

In the C-H functionalization step the *unsymmetrical* diaryl λ^3-iodane **2.15** is formed, and then it undergoes a ligand exchange reaction with an incoming nucleophile to furnish a new iodine(III) intermediate **2.16** (Fig. 2.6.). If the nucleophile is phenolate or azide, then the corresponding diaryl-λ^3-iodane can be obtained and isolated in a pure form (for phenolate–containing iodane **2.3**, see Fig. 2.1.). The structure of the azide containing iodane **2.41** was confirmed by using X-ray analysis (Fig. 2.8.).

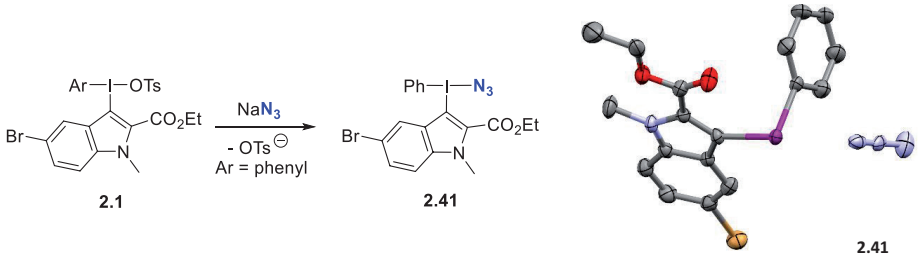

Figure 2.8. **Ligand exchange reaction in diaryl-λ^3-iodane 2.1.**

Kinetic studies of C-H azidation reaction show that CuOTf-catalyzed iodane **2.41** conversion to 3-azidoindole **2.42** is first–order in Cu(I) catalyst, and zeroth–order reaction with respect to the azide ion. Hence, Cu(I) is involved in the rate limiting step of the catalytic cycle, but azide transfer from the iodine(III) center to the indole heterocycle is an intramolecular process. One of the most plausible mechanisms of the C-H azidation reaction includes oxidative addition of azidoiodane **2.41** to the Cu(I) catalyst, followed by reductive elimination of azide **2.42** (Fig. 2.9).

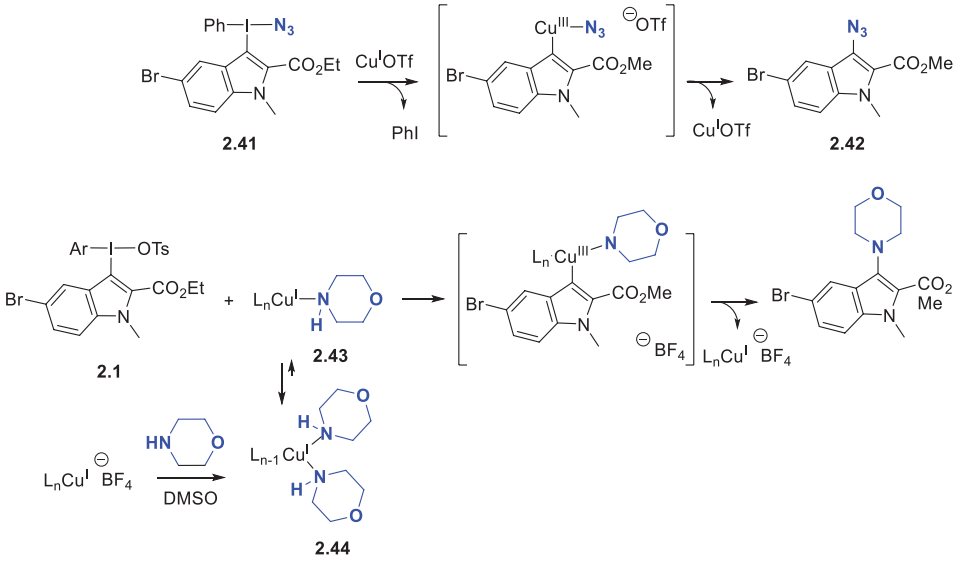

Figure 2.9. **Plausible mechanisms of C-H azidation and amination reactions.**

Formation of a new diaryl-λ^3-iodanes was not observed in the reaction of iodine(III) intermediate **2.1** with amine nucleophiles. Apparently, iodine(III) intermediated containing an amine ligand are too unstable to be isolated and characterized. It is possible that amine ligand containing diaryl-λ^3-iodanes are not formed at all, and that the formation of C-N bond follows another mechanism. The last assumption is confirmed by the kinetic studies, which show that $(CuOTf)_2$-catalyzed C-H amination reaction of diaril-λ^3-iodane **2.1** (Ar=mesityl) with morpholine is the first–order in Cu(I) catalyst, first–order in morpholine, and zeroth–order with respect to iodane **2.1**. These results show that Cu(I) and morpholine are involved in the rate limiting step of the catalytic cycle, whereas all the steps where iodane **2.1** is involved are fast. Likely, copper(I)-amine complex **2.43** is formed in the reaction of the Cu(I) catalyst with morpholine, and this complex is in an equilibrium with the corresponding *bis*-amine complex **2.44**. Assuming that the complex **2.44** is a resting state[20] of the catalyst, dissociation of morpholine under equilibrium conditions would produce a catalytically active copper(I)-morpholine complex. Thus, the putative C-H amination mechanism suggests that diaryl-λ^3-iodane **2.1** undergo reaction with morpholine-Cu(I) catalyst rather than with morpholine (Fig. 2.9).

2.2.3. Selectivity of the Ligand Coupling in the Reductive Elimination

Mesityl ligand–containing iodine(III) reagents **2.14** (Ar=mesityl; Fig. 2.6) were used in the synthesis of *unsymmetrical* diaryl-λ^3-iodane intermediates **2.15** (Fig. 2.6) in order to achieve high selectivity in the coupling reaction between a nucleophile (phenolate, azide, amine) and (hetero)aromatic ligands. The transfer of the mesityl group to transition metals is prevented by the steric hindrance. Therefore the mesityl group is often used as a dummy ligand in the reactions between a hypervalent iodine(III) compound and transition metals. Unfortunately, the use of the mesityl ligand in the C-H amination reaction of aromatic compounds (e.g., xylene **2.34**) provided moderate selectivity (**2.46**:**2.47**=5:2; Fig. 2.10).

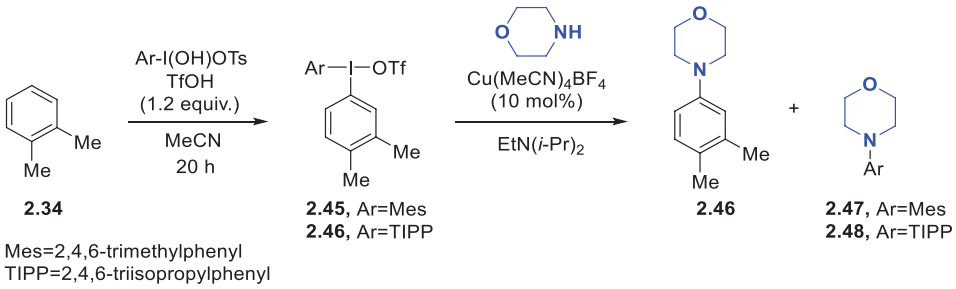

Figure 2.10. **Dependence of the regioselectivity of C-H amination on the ligand structure.**

Sterically more hindered iodine(III) compounds containing 1,3,5-triisopropyphenyl ligand (TIPP) were used instead of the mesityl ligand to improve both the ligand coupling selectivity and yield of the desired C-H amination product. The employment

of TIPP ligands containing iodine(III) reagents provided significantly higher selectivity in ligand coupling reaction (**2.46**:**2.48**=98:2; Fig.) and thereby increased the yield of the desired product.

2.2.4. Scope of the Developed C-H Functionalization and Application Example

The sequential multi-step one-pot C-H functionalization method is suitable for C–O and C–N bond formation in relatively electron-rich heteroaromatic and aromatic systems (Fig. 2.11). Products of the copper(I)-catalyzed azidation reaction (heteroaromatic azides) turned out to be relatively unstable and their isolation in a pure form was difficult. Therefore, the formed azides were reduced to corresponding amines or converted to 1,2,3-triazoles in a copper(I)-catalyzed reaction with acetylenes.

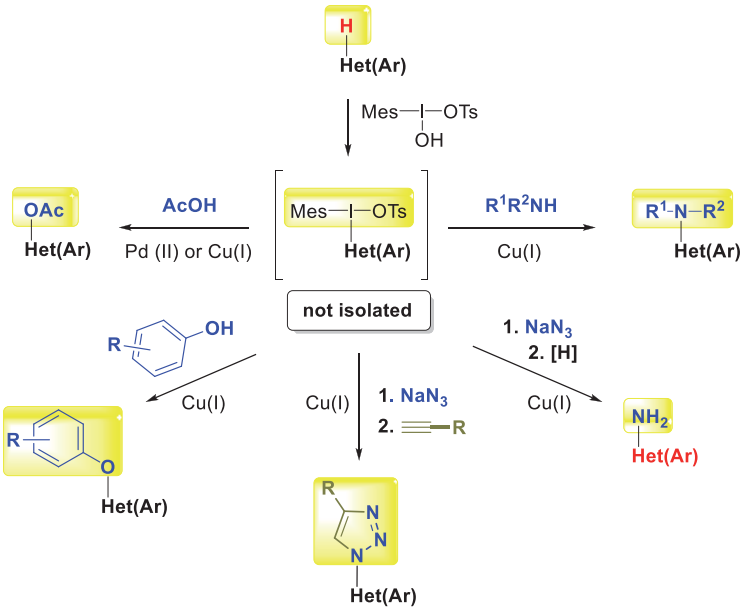

Figure 2.11. **Scope of the developed C-H functionalization methods.**

To show that the developed C-H functionalization methods is suitable for the late stage functionalization in the (hetero)aromatic systems, the antibiotic *linezolid* was synthesized. The morpholine moiety was introduced into the aromatic system in the final step of the synthesis of linezolid (Fig. 2.12).

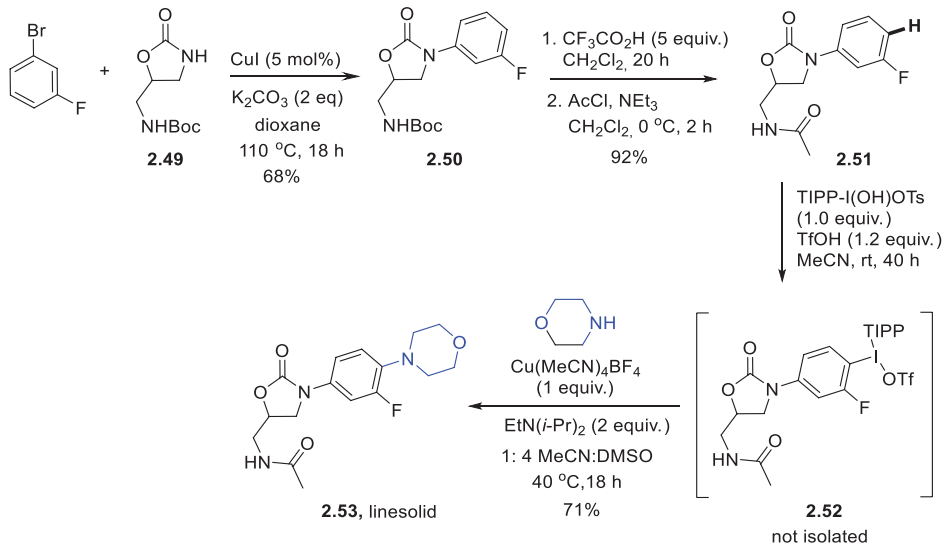

Figure 2.12. **The synthesis of linezolid.**

The commercially available oxazolidinone **2.49** was *N*-arylated in the presence of a copper(I) catalyst in the first step of the synthesis. Cleavage of the *N*-Boc protecting group in **2.50** and subsequent *N*-acetylation furnished product **2.51**, a substrate for the C-H amination reaction. To achieve full conversion in the synthesis of the *unsymmetrical* diaryl-λ^3-iodane **2.52**, a relatively long time (40 h) was necessary. Stoichiometric amount of $Cu(MeCN)_4BF_4$ complex was required in the reaction of morpholine with iodine(III) intermediate **2.52**. Linezolid **2.53** was isolated in 71% yield (Fig. 2.12.). It should be emphasized that the developed method is very suitable for the introduction of a broad scope of amines in the linezolid scaffold **2.51** at the late stage of the synthesis. The methodology can also be used in the synthesis of a library of linezolid analogs.

CONCLUSIONS

1) The formation of unsymmetrical diaryl-λ^3-iodanes proceeds with the excellent regioselectivity, which is consistent with that of an electrophilic aromatic substitution reaction. When aromatic compounds are used, λ^3-iodanes are formed at the *para*-position to the strongest electron-donating substituent;
2) Toluene represents a reactivity borderline: arenes that are less electron-rich than toluene did not react with the hypervalent iodine(III) reagents, and the corresponding unsymmetrical diaryl-λ^3-iodanes are not formed;
3) Transition metal (Pd and Cu) catalysts alter the selectivity of ligand coupling reaction in unsymmetrical diaryl-λ^3-iodanes: nucleophilic ligand in hypervalent bond will react either with a sterically less hindered or with the most electron-rich of the two aryl ligands. The most suitable catalysts are inexpensive and non-toxic Cu(I) salts (CuOTf and $Cu(MeCN)_4BF_4$ as well as $Pd(OAc)_2$;
4) It is possible to improve selectivity of the ligand coupling by increasing the steric hindrance of a non-transferrable ligand. The selectivity of the ligand coupling under transition metal-catalyzed conditions increases in the following order

   phenyl< 1,3,5-trimethylphenyl < 1,3,5-triisopropylphenyl;

5) The developed methodology for C-H functionalization of electron-rich (hetero) aromatic compounds is suitable for the late-stage modification of the potential drug-like structures. This is confirmed by the example of the late-stage C-H amination of antibiotic linezolid.

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Iodonium Salts Are Key Intermediates in Pd-Catalyzed Acetoxylation of Pyrroles

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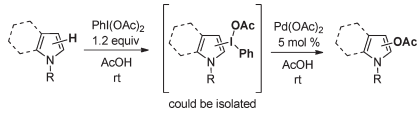
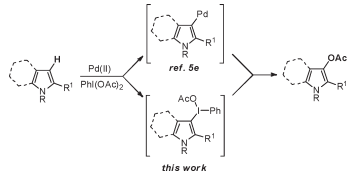
ABSTRACT



A mild, room-temperature Pd-catalyzed acetoxylation of pyrroles with phenyliodonium acetate is described. The acetoxylation was found to proceed via the initial formation of pyrrolyl(phenyl)iodonium acetates, which were converted to acetoxypyrroles in the presence of $Pd(OAc)_2$. The acetoxylation could also be carried out as a one-pot sequential procedure without the isolation of the intermediate iodonium salts.

Transition metal catalyzed selective C–H oxidation is an efficient methodology for the construction of C–O bonds.[1] The regioselectivity of the C–H activation/oxidation in aromatic systems usually is controlled by suitable *ortho*-directing groups.[2] Intriguingly, in contrast to the many examples of C–O bond formation in benzene rings,[3] the direct acetoxylation of heterocycles is much less explored.[4] Thus, there are only a few reports on direct acetoxylation of heterocycles, and the scope of substrates is limited to indoles[5] and uracil.[6] It should be noted that the regioselectivity of C–O bond formation in heterocycles typically is controlled by the inherent reactivity of a given heterocyclic system and, consequently, there is no need for the *ortho*-directing group.

Direct acetoxylation examples frequently employ $Pd(OAc)_2$ as a catalyst and $PhI(OAc)_2$ as a terminal oxidant in acetic acid, conditions that have been developed by Crabtree.[7] Mechanistic studies evidence that the Pd-catalyzed direct acetoxylation involves palladation of an aryl C–H bond with Pd(II) species as the first step,[8] which is followed by oxidation to dinuclear Pd(III) complexes[9] and, finally, product forming reductive elimination. By analogy, carbopalladation via C–H activation was considered to be the initial step also in Pd-catalyzed acetoxylation of indoles (eq 1).[5e]



(1)

The present report on a selective oxidation of substituted pyrroles[10] expands the scope of heterocycles for the

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(6) Lee, H. S.; Kim, S. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2010**, *31*, 238.

(7) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A* **1996**, *108*, 35.

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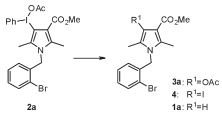
Pd-catalyzed acetoxylation reaction. Also, we provide evidence that the acetoxylation of electron-rich heterocycles such as pyrroles and indoles under Crabtree conditions most likely occurs via the initial formation of heteroaryliodonium acetates (eq 1).[11] The latter are transformed into an acetoxylated product in the presence of a Pd catalyst.

Initially, Crabtree acetoxylation conditions were examined for synthesis of acetoxypyrroles and the progress of the reaction was followed by NMR methods. Thus, stirring the pyrrole **1a** with $Pd(OAc)_2$ (5 mol %) and $PhI(OAc)_2$ (2 equiv) in AcOH-d_4 showed complete conversion within 2 h at ambient temperature.[12] Two sets of signals in a 3.5:1 ratio were observed in the ^1H NMR spectrum of the reaction mixture. The minor set of signals corresponded to acetoxypyrrole **3a**, whereas the major set of signals was assigned to a structure of pyrrolyliodonium acetate **2a** based on ^1H NMR, ^{13}C NMR, MS data and X-ray crystallographic analysis of purified **2a**.

The iodonium acetate **2a** was stable in AcOH-d_4 solution at rt (entry 1, Table 1). However, in the presence of 5 mol % $Pd(OAc)_2$ in AcOH-d_4, **2a** was converted into the target acetoxypyrrole **3a** (90% yield) within 18 h (entry 2). Acetonitrile was equally efficient to AcOH, affording **3a** in 91% yield (entry 3). Additional experiments were performed to investigate the reactivity of iodonium salt **2a**. Heating of **2a** without the Pd catalyst yielded a mixture of products **3a**, **4**, and the starting **1a** (entry 4). Interestingly, only unreacted **2a** was observed after prolonged heating in $(CF_3)_2CHOH$, a solvent of choice for oxidative nucleophilic acetoxylation of alkylphenyl ethers (entry 5).[13] $PtCl_2$ was inferior to $Pd(OAc)_2$ as a catalyst[5e] (entry 6), whereas $PtCl_4$ did not catalyze the conversion of **2a** (entry 7). Likewise, $BF_3{\bullet}OEt_2$[14] in DCM (entry 8) and $Cu(OTf)_2$ in DCM[15] were not efficient as catalysts (entries 8, 9), whereas addition of TMS-OTf[16] resulted in the formation of an inseparable mixture of products (entry 10).

Table 1. Reactivity of Arylpyrrolyliodonium Acetate **2a**



entry	catalyst (mol %)	solvent	*t* (°C)	time (h)	products (yield, %)
1	–	AcOH	rt	18	**2a**
2	$Pd(OAc)_2$ (5)	AcOH	rt	18	**3a** (90%)
3	$Pd(OAc)_2$ (5)	MeCN	60	18	**3a** (91%)
4	–	AcOH	100	24	**3a** (45%) + **4** (20%) + **1a** (27%)
5	–	HFIP	100	18	**2a**
6	$PtCl_2$ (5)	AcOH	80	48	**3a**:**1a** = 3:2
7	$PtCl_4$ (5)	AcOH	80	48	**2a**
8	$BF_3{\bullet}OEt_2$ (400)	CH_2Cl_2	rt	3	**2a**
9	$Cu(OTf)_2$ (10)	CH_2Cl_2	35	24	**2a**
10	TMS-OTf (200)	HFIP	rt	2	products mixture

A series of pyrrolyliodonium acetates **2b**–**k** was subsequently prepared in the reaction of pyrroles **1b**–**k** with 1.2 equiv of $PhI(OAc)_2$ in AcOH at ambient temperature (63–79% yields; see Table 2). The iodonium acetates **2b**–**k** were sufficiently stable to be isolated and characterized,[17] and they can be stored in the freezer for several months. To the best of our knowledge, pyrrolyl-3-iodonium acetates have not been previously prepared in a direct electrophilic substitution of pyrrole.[18]

The yields of iodonium salts **2a**–**k** were found to be sensitive to the electronic properties of substituents on the pyrrole ring.[19] Iodonium acetates were formed from *N*-unsubstituted pyrroles **2h,k** (entries 8,11, Table 2). The regioselectivity of pyrrolyliodonium salt formation apparently is a result of the combined directing effects of pyrrole substituents.[20] Nevertheless, there is a strong preference for the formation of iodonium salts at the α-position (entries 2, 3, 9, 10),[21] and β-pyrrolyliodonium salts could be obtained only for 2,5-disubstuted heterocycles **1a,e**–**h,k** (entries 1, 5–8, 11, Table 2).

In the presence of 5 mol % $Pd(OAc)_2$ in AcOH solution at ambient temperature iodonium salts **2a**–**k**

(8) It has been shown that cyclopalladation is the rate-limiting step of the acetoxylation reaction: Stowers, K. J.; Sanford, M. S. *Org. Lett.* **2009**, *11*, 4584.

(9) (a) Powers, D.; Ritter, T. *Top. Organomet. Chem.* **2011**, *35*, 129. (b) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302.

(10) (a) The 3-hydroxypyrrole subunit is incorporated into Obatoclax, an experimental drug candidate for the treatment of various types of cancer: *Drugs Future*, **2007**, *32*, 228. Substituted 3-hydroxypyrroles have also been employed: (b) as anti-tumor agents: Cholody, W. M.; Petukhova, V.; O'Brien, S.; Ohler, N.; Pikul, S. WO 011675 *A1*, 2005; *Chem. Abstr.* **2005**, *142*, 197868. (c) in the design of DNA-binding ligands: Wellenzohn, B.; Loferer, M. J.; Trieb, M.; Rauch, C.; Winger, R. H.; Mayer, E.; Liedl, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 1088.

(11) Consequently, the acetoxylation with $PhI(OAc)_2$ does not involve a C–H activation step by a Pd catalyst. The role of transition metal catalysts has recently been reinvestigated also in other $PhI(OAc)_2$ mediated reactions; see: (a) Kang, Y.-B.; Gade, L. H. *J. Am. Chem. Soc.* **2011**, *133*, 3658. (b) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996.

(12) The use of $Pd(OAc)_2$ together with other oxidants such as $PhCO_3tBu$ (2 equiv, 65 °C, Ac_2O, 21 h), *m*-CPBA (2 equiv, 100 °C, AcOH, 2 h), $K_2S_2O_8$ (2 equiv, 100 °C, AcOH, 2 h), and Oxone (2 equiv, 100 °C, AcOH, 2 h) did not afford the acetoxylated pyrrole **3a**.

(13) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684.

(14) Dohi, T.; Morimoto, K.; Takenaga, N.; Goto, A.; Maruyama, A.; Kiyono, Y.; Tohma, H.; Kita, Y. *J. Org. Chem.* **2007**, *72*, 109.

(15) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

(16) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto., K.; Fujioka, H.; Kita, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 3334.

(17) The majority of solid aryliodonium acetates **2b**–**k** are hygroscopic and decompose at temperatures above 25 °C. However, they are stable in acetic acid solutions.

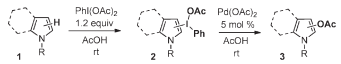
(18) Single report on preparation of pyrrolyl-3-iodonium triflates from 3-trimethylsilylpyrrole: Liu, J.-H.; Chan, H.-W.; Xue, F.; Wang, Q.-G.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **1999**, *64*, 1630.

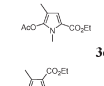
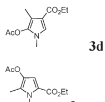
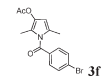
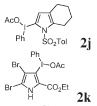
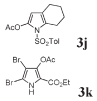
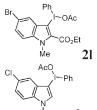
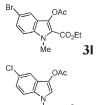
(19) Correlation between yields of phenyliodonium salts and Hammett σ constants of substituents has been reported: Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775. See also the Supporting Information, p S26.

(20) For substituent effect on regioselectivity of S_EAr reactions of pyrroles, see: Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; John Wiley & Sons: Chichester, 2010; pp 289–323.

(21) For other examples, see: (a) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775. (b) Reference 16. (c) Martin-Santamaria, S.; Carroll, M. A.; Carroll, C. M.; Carter, C. D.; Pike, V. W.; Rzepa, H. S.; Widdowson, D. A. *Chem. Commun.* **2000**, 649.

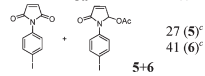
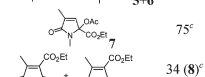
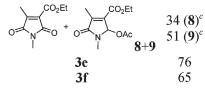
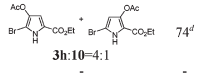
Table 2. Acetoxylation of Pyrroles **1a**–**k** and Indoles **1l**–**m** via Isolation of Intermediate Iodonium Salts **2a**–**m**



entry	iodonium salt	time (h)	yield (%)	product	time (h)	yield[a] (%)
1	 **2a**	6	78	 **3a**	18	90
2	 **2b**	3	77	 **3b**	1	85
3	 **2c**	6	72	 **3c**	3	79
4	 **2d**	3	79	 **3d**	3	78
5	 **2e**	6	65	 **3e**	18	79
6	 **2f**	3	79	 **3f**	18	71
7	 **2g**	18	63	 **3g**	18	73
8	 **2h**	18	73	 **3h**	18	79
9	 **2i**	3	71	 **3i**	18	67
10	 **2j**	18	71	 **3j**	18	71
11	 **2k**	18	79	 **3k**	1	74[b]
12	 **2l**	18	79	 **3l**	1	81[b]
13	 **2m**	6	66	 **3m**	3	73

[a] Yields for the conversion from **2** to **3**. [b] Heating at 100 °C.

Table 3. One-Pot Sequential Procedure vs Crabtree Conditions

entry	pyrrole	One-pot[a] product	yield (%)	Crabtree conditions[b] product	yield (%)
1	**1a**	**3a**	92	**3a**	85
2	**1b**	**3b**	56	 **5**+**6**	27 (**5**)[c] 41 (**6**)[c]
3	**1c**	**3c**	80	 **7**	75[c]
4	**1d**	**3d**	77	 **8**+**9**	34 (**8**)[c] 51 (**9**)[c]
5	**1e**	**3e**	86	**3e**	76
6	**1f**	**3f**	60	**3f**	65
7	**1g**	**3g**	50	-	-
8	**1h**	**3h**	74	 **3h**:**10**=4:1	74[d]
9	**1i**	**3i**	42	-	-
10	**1j**	**3j**	41	-	-
11	**1k**	**3k**	69	**3k**	41[c,e]
12	**1l**	**3l**	86	**3l**	77[f]
13	**1m**	**3m**	70	**3m**	51

[a] Pyrrole **1** (1 equiv) and $PhI(OAc)_2$ (1.2 equiv) were stirred in AcOH at rt for 3–18 h (see Table 2 for time; the formation of **2** was monitored by ^1H NMR), then $Pd(OAc)_2$ (0.05 equiv) was added, and stirring at rt was continued for 1–18 h (see Table 2). [b] Pyrrole **1** (1 equiv), $PhI(OAc)_2$ (1.3 equiv), and $Pd(OAc)_2$ (0.05 equiv) were heated in AcOH at 100 °C for 1 h. [c] 2.3 equiv of $PhI(OAc)_2$. [d] Yield of a 4:1 mixture of **3h** and **10**. [e] Heating at 100 °C for 3 h. [f] Reference 5e.

were readily converted into the target acetoxypyrroles **3a**–**k** (see Table 2). A simple workup and purification by chromatography afforded pure **3a**–**k** (Table 2). The Pd-catalyzed acetoxylation conditions are compatible with the presence of bromine (entries 8, 11) and even iodine (entry 2). *N*-Alkyl, *N*-aryl, *N*-benzoyl, *N*-benzyl, *N*-tosyl, and *N*-carbamoyl are tolerated at the pyrrole nitrogen (Table 2).

We have found that the acetoxypyrroles **3a**–**k** could also be synthesized in a sequential one-pot approach without isolation of the intermediate iodonium salts **2a**–**k** (see Table 3). Accordingly, $Pd(OAc)_2$ was added to the reaction mixture after the corresponding iodonium acetate has been formed.[22] In general, the sequential one-pot approach afforded higher yields of **3a**–**k** compared to the two-step reaction. Importantly, the original Crabtree[7] conditions are inferior to the sequential one-pot approach. Thus, not only the yields are substantially lower (Table 3, entries 1, 5, 8, 11, 12) but also the formation of overoxidation products is more pronounced. For example, acetoxylation of pyrroles **1b**–**d** under Crabtree conditions (entries 2–4, Table 3) afforded mixtures of pyrrole-2,5-diones **5,8** and 5-functionalized pyrrolidin-2-ones **6,7,9**. γ-Lactams such as **6,7,9** have been found in a wide range of biologically active natural products.[23]

The initial formation of salts **2a**–**k** in the Pd-catalyzed acetoxylation reaction prompted us to hypothesize that the previously reported acetoxylation of indoles under similar conditions ($Pd(OAc)_2$ and $PhI(OAc)_2$)[5e] may also proceed via the intermediate indolyliodonium acetates. Indeed, treatment of indoles **1l,m** with $PhI(OAc)_2$ in AcOH afforded C3-iodonium salts **2l,m** which were stable in AcOH-d_4 solution and could be isolated.[24]

(22) The formation of iodonium acetates **2a**–**k** was controlled by ^1H NMR. The addition of $Pd(OAc)_2$ early on resulted in the formation of overoxidation products.

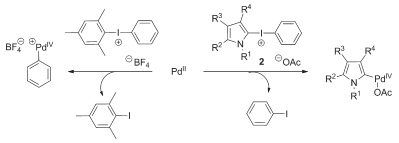
(23) For a review, see: Nay, B.; Riache, N.; Evanno, L. *Nat. Prod. Rep*. **2009**, *26*, 1044.

(24) The structures of **2a** and **2l** were confirmed by X-ray analysis; see the Supporting Information, pp S29 and S30.

Furthermore, salts **2l,m** were smoothly converted into acetoxyindoles **3l,m** in the presence of $Pd(OAc)_2$ (5 mol %) (see Table 2, entries 12, 13). The sequential one-pot approach afforded higher yields of **3l** compared to the Crabtree conditions (86% vs 77%, Table 3, entry 12).

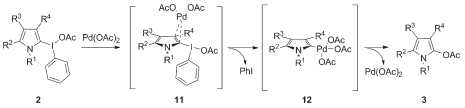
The Pd-catalyzed formation of C−O bonds from iodonium acetates **2a**−**m** showed high regioselectivity for the sterically more bulky heterocycle ring, and *O*-acetylphenol formation was not observed. Assuming that acetoxylation occurs via the initial transfer of pyrroles and indoles from the iodonium salts **2** to Pd, the observed regioselectivity is striking, because the less hindered aryl group usually is transferred from nonsymmetrical diaryliodonium salts (such as [Ar-I-Mes]BF_4) to Pd (Scheme 1).[25]

Scheme 1. Regioselectivity in the Reaction of Nonsymmetrical Iodonium Salts with Palladium



Apparently, electronic preferences rather than steric factors control the acetoxylation regioselectivity of salts **2**. Thus, it has been demonstrated that in Pd(II)-catalyzed reactions the more electron-rich Ar moiety is selectively transferred from unsymmetrical diaryliodonium salts [Ar-I-Ar′]BF_4 to a Pd catalyst.[26,27] The high regioselectivity of the pyrrole and indole ring transfer to a Pd catalyst, presumably, is ensured by η^2-coordination of an iodonium substituted double bond of the more electron-rich pyrrolyliodonium moiety to the Pd(II) species (complex **11**, Scheme 2).[28] Subsequent oxidative addition would generate a transient pyrrolyl−Pd(IV) complex **12**, which undergoes C−O bond forming reductive elimination.

Scheme 2. Proposed Mechanism for Acetoxylation of Pyrroles



The acetoxylation of pyrroles presumably involve a Pd(II)/Pd(IV) or Pd(II)/Pd(III) catalytic cycle. However, the Pd(0)/Pd(II) catalytic cycle cannot be ruled out, as evidenced by the "mercury drop" test.[29] Thus, addition of a large excess (> 300 equiv) of metallic Hg to a mixture of iodonium acetate **2a** and $Pd(OAc)_2$ (5 mol %) in AcOH resulted in complete inhibition of the acetoxylation (< 5% of acetoxypyrrole **3a** was formed).[30] Additional work is ongoing to elucidate the mechanism of the Pd-catalyzed conversion of **2** to **3**.

In summary, a series of stable pyrrolyl(aryl)iodonium and indolyl(aryl)iodonium acetates **2a**−**m** have been prepared and characterized. The formation of intermediate iodonium salts of pyrroles **2a**−**k** and indoles **2m,l** under the acetoxylation conditions as well as their Pd-catalyzed conversion to oxidized heterocycles **3a**−**l** indicate that iodonium salts **2a**−**l** are actual intermediates in the acetoxylation reaction. Consequently, we propose that the formation of iodonium salts **2** is the first step in the catalytic cycle for the acetoxylation of pyrroles and indoles. Such a mechanism differs from the closely related Pd-catalyzed C2-arylation of pyrroles and indoles with diaryliodonium salts, which proceeds via the initial carbopalladation of the pyrrole ring.[31] Further studies to expand the scope of heterocycles in the Pd-catalyzed regioselective acetoxylation reaction via iodonium acetates are ongoing in our laboratory.

Acknowledgment. This work was supported by the European Regional Development Fund (No. 2DP/2.1.1.1.0/10/APIA/VIAA/066).

Supporting Information Available. Experimental procedures, products characterization, copies of ^1H and ^{13}C NMR spectra, and X-ray crystallographic data for iodonium salts **2a,l** (CIF files). This material is available free of charge via the Internet at http://pubs.acs.org.

(25) The presence of a bulky mesityl group in iodonium salts [Mes-I-Ar]X ensured the selective transfer of the smaller Ar group in Pd-catalyzed arylations: (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (b) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234. For the analogous use of a nontransferrable 2,4,6-tri-isopropylphenyl group, see:Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

(26) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924 and references cited therein.

(27) Decomposition of [Mes-I-Ph]OAc under Crabtree acetoxylation conditions ($Pd(OAc)_2$, AcOH, 100 °C, 18 h) was moderately selective for the formation of Mes-OAc (ratio Mes-OAc/Mes-I = 3.4:1).

(28) (a) Related η^2-coordination of 2-tributylstannylfurane to Pd(II) followed by tin-to-palladium transmetallation of the furyl group has been observed: Cotter, W. D.; Barbour, L.; McNamara, K. L.; Hechter, R.; Lachicotte, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 11016. (b) For related stable η^2-arylgold(I) complexes, see: Herrero-Gómez, E.; Nieto-Oberhuber, C.; Salomé, L.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5455.

(29) (a) Anton, D. R.; Crabtree, R. H. *Organometallics* **1983**, *2*, 855. (b) Foley, P.; DiCosimo, R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 6713.

(30) The formation of palladium black has always been observed in the late stages of the acetoxylation.

(31) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972.

II

Lubriks, D.; Sokolovs, I.; Suna, E.
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Indirect C−H Azidation of Heterocycles via Copper-Catalyzed Regioselective Fragmentation of Unsymmetrical λ^3-Iodanes

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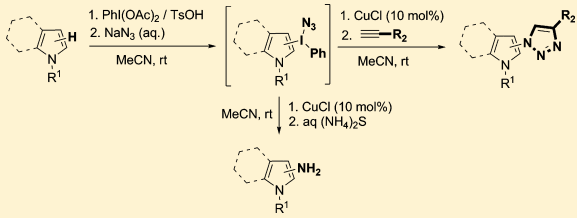
Supporting Information



ABSTRACT: A C−H bond of electron-rich heterocycles is transformed into a C−N bond in a reaction sequence comprising the formation of heteroaryl(phenyl)iodonium azides and their in situ regioselective fragmentation to heteroaryl azides. A Cu(I) catalyst ensures complete regiocontrol in the fragmentation step and catalyzes the subsequent 1,3-dipolar cycloaddition of the formed azido heterocycles with acetylenes. The heteroaryl azides can also be conveniently reduced to heteroarylamines by aqueous ammonium sulfide. The overall C−H to C−N transformation is a mild and operationally simple one-pot sequential multistep process.

INTRODUCTION

Symmetrical diaryliodonium salts have found numerous applications as electrophilic arylating reagents in both transition-metal-catalyzed and metal-free reactions with carbon and heteroatom nucleophiles.[1] Unsymmetrical diaryliodonium salts, however, are less frequently employed, because the presence of two different aromatic moieties in λ^3-iodanes can potentially lead to the formation of product mixtures in the reactions with nucleophiles. Nevertheless, regiocontrol can be achieved by differentiation of electronic and steric properties of aromatic moieties. Thus, a nucleophile would preferentially react with the more electron-deficient and/or sterically hindered *ortho*-substituted aromatic ring of unsymmetrical diaryliodonium salts (Figure 1).[2] In the meantime, regioselective reaction of nucleophiles with electron-rich aromatic or heteroaromatic moieties of unsymmetrical diaryl-λ^3-iodanes is a challenging task. We envisioned, however, that the desired regioselectivity of nucleophile attack can be ensured by a transition-metal catalyst, because in the catalytic cross-coupling reactions electron-rich[3] and/or less sterically hindered[4] aryl moieties are selectively transferred from unsymmetrical iodonium salts to the transition metal (Figure 1).

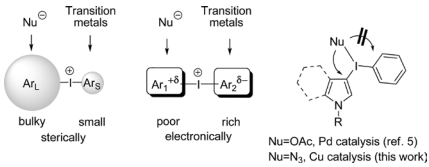


Figure 1. Regioselectivity in the reactions of nonsymmetrical iodonium salts.

We have recently demonstrated that the regioselectivity of acetoxylation of heteroaryl(phenyl)iodonium acetates can be directed to the more electron-rich heteroaryl moiety by a Pd(II) catalyst.[5] We reasoned that use of other counterions instead of acetate would provide straightforward access to differently substituted heterocycles by the transition-metal-catalyzed regioselective fragmentation of unsymmetrical heteroaryliodonium species. Herein we report a one-pot sequential procedure for C−H to C−N transformation in electron-rich heterocycles (pyrroles, pyrrolopyridines, thienopyrroles, pyrrolopyrimidines, and uracil) comprising in situ preparation of heteroaryl(phenyl)iodonium azides and their Cu-catalyzed conversion to heteroaryl azides. The formed azides are not sufficiently stable to be isolated; however, they can be in situ reduced to heteroaromatic amines. The developed one-pot four-step C−H to C−N transformation sequence is a mild and convenient alternative to the transition-metal-catalyzed direct C−H amination of arenes[6] and heteroarenes,[7,8] which usually requires elevated temperatures to proceed. The in situ formed heteroaryl azides can also undergo Cu-catalyzed azide−alkyne cycloaddition to furnish 1,2,3-triazoles,[9] thus allowing for the

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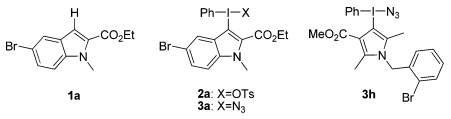
direct ligation of heterocycles to biomolecular frameworks via a triazole linker, an approach that is widely used in bioconjugate chemistry[10] for labeling and modification of oligonucleotides[11] and peptidomimetics.[12] The developed C−H azidation/1,3-dipolar cycloaddition sequence is suitable also for use in discovery of lead compounds by target-directed synthesis[13] as well as in the design of novel peptidomimetics.[14] Furthermore, 1,2,3-triazoles can be employed for synthesis of other heterocyclic systems.[15]

RESULTS AND DISCUSSION

At the outset of the investigation, we examined the regioselectivity of fragmentation of indolyl(phenyl)iodonium azide **3a**. The iodonium salt **3a** was synthesized by the reaction of indole **1a** with a mixture of $PhI(OAc)_2$ and TsOH,[16] followed by exchange of tosylate anion for azide in the intermediate **2a**. The formed iodonium azide **3a** was unstable, and in the crystalline form it slowly decomposed to iodoindole **5a** even at −18 °C. Nevertheless, the indolyl azide **3a** as well as its pyrrole analogue **3h** could be characterized, and their structures were confirmed by X-ray crystallographic analysis (Table 1).[17] In the crystal lattice azides **3a,h** exist in a

Table 1. Selected Crystallographic Parameters for Iodonium Azides 3a,h

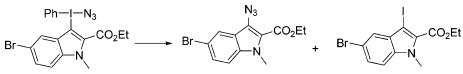


	λ^3-iodane	N_3–I–C(Het) angle (deg)	I–N_3 distance (Å)	I–C(Ph) distance (Å)	I–C(Het) distance (Å)
3a	174.1	2.813	2.112	2.083	
3h	177.3	2.837	2.129	2.064	

characteristic slightly distorted T-shaped geometry with the heterocycle in the equatorial position and Ph moiety and azide anion in axial positions (for selected crystallographic parameters see Table 1). Notably, I–N bonds in the azides **3a,h** are considerably longer than hypervalent I–N bonds in structurally related azidobenziodoxole[18] (2.182 Å) and polymeric iodine azide (2.26–2.30 Å).[19] Furthermore, the distance between the hypervalent iodine in **3h** and the azide anion (2.837 Å, Table 1) is much longer than that between the iodine of the phenyl(pyrrolyl)iodonium moiety of **3h** and the acetate anion (2.592 Å).[5] Apparently, the long hypervalent I–N bond possesses partial ionic character,[20] which accounts for the low stability of iodonium azides **3a,h**.

In MeCN and CH_2Cl_2 solutions at room temperature the iodonium azide **3a** spontaneously decomposed to 3-iodoindole **5a** and phenyl azide (see Table 2, entries 1 and 2). Importantly, the desired indolyl azide **4a** was not formed in MeCN and CH_2Cl_2. The regioselectivity of the noncatalyzed fragmentation of iodonium salt **3a** apparently is controlled by electronic factors, as evidenced by the delivery of the azide nucleophile to the relatively more electron-deficient phenyl ring rather than to the electron-rich indole moiety of **3a**.[21] Notably, λ^3-iodane **3a** was stable in DMSO (entry 3) at room temperature. The addition of $Pd(OAc)_2$ (5 mol %) did not alter the course of the reaction (entries 4 and 5), whereas Cu salts completely reversed the fragmentation regioselectivity, and the iodonium

Table 2. Fragmentation of Indolyliodonium Azide 3a



entry	catalyst (concn, mol %)	solvent	time	conversion[a,b] %	**4a**:**5a** ratio[b]
1	none	MeCN	60 h	35[c]	1:99
2	none	CH_2Cl_2	3 h	70	1:99
3	none	DMSO	3 h	<5	
4	$Pd(OAc)_2$ (5)	MeCN	24 h	32	1:5
5	$Pd(OAc)_2$ (5)	CH_2Cl_2	3 h	35	1:99
6	$Cu(OTf)_2$ (10)	CH_2Cl_2	3 h	60	9:1
7	CuOTf·PhH (10)	CH_2Cl_2	30 min	100	9:1
8	CuOTf·PhH (10)	MeCN	30 min	87	9:1
9	CuOTf·PhH (10)	toluene	30 min	85	4:1
10	CuOTf·PhH (10)	THF	30 min	60	5:1
11	CuOTf·PhH (10)	DMSO	30 min	45	9:1
12	CuCl (10)	CH_2Cl_2	5 min	100	9:1
13	CuCl (10)	MeCN	5 min	100	12:1
14	CuCl (10)	DMSO	30 min	78	12:1
15	CuCl (10)	MeCN–DMSO (1:1)	15 min	85	10:1
16	TfOH (200)	CH_2Cl_2	3 h	23	1:99
17	$Zn(OTf)_2$ (10)	CH_2Cl_2	3 h	27	1:99
18	$Sc(OTf)_3$ (10)	CH_2Cl_2	3 h	20	1:99
19	$(Ph_3P)AuCl$ (10)	CH_2Cl_2	3 h	45	1:99

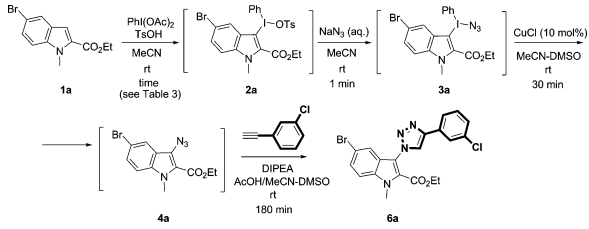
[a]Reactions at room temperature. [b]Determined by LC–MS assay. [c]Conversion of 100% (**4a**:**5a** = 1:99) after 30 min at 80 °C.

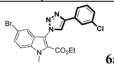
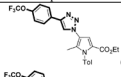
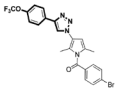
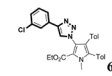
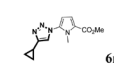
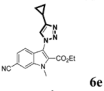
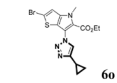
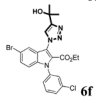
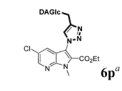
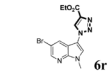
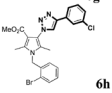
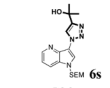
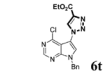
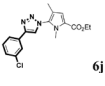
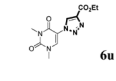
azide **3a** was smoothly converted to the desired indolyl azide **4a** (entries 6–15).

Copper catalysts considerably decreased the reaction time, with CuCl and CuOTf in CH_2Cl_2 being the most efficient (entries 7 and 12). Interestingly, both Cu(I) and Cu(II) salts can be used; however, the Cu(I) species ensured faster reaction (entry 7 vs entry 6). Other solvents either retarded the reaction (entries 10, 11, and 14) or deteriorated the regioselectivity (entries 9 and 10). It should be noted that the conversion of **3a** was faster in CH_2Cl_2 compared to MeCN (entry 2 vs entry 1 and entry 7 vs entry 8). Lewis acids such as $(Ph_3P)AuCl$, $Zn(OTf)_2$, and $Sc(OTf)_3$ as well as TfOH were completely inefficient as catalysts (entries 16–19). Consequently, CuCl (10 mol %) was chosen for all subsequent experiments.

The observed high regioselectivity of the Cu(I)-catalyzed fragmentation of iodonium salt **3a** to azide **4a** (**4a**:**5a** = 9:1) in CH_2Cl_2 is slightly lower than the regioselectivity of the alternative noncatalyzed formation of **5a** from **3a** (**4a**:**5a** = 1:99). The determined initial rates of the noncatalyzed fragmentation of **3a** to iodide **5a** in CH_2Cl_2 (rate coefficient $k = 9 \times 10^{-5}$ s^{-1}, CH_2Cl_2-d_2, 23 °C, and reaction half-life $t_{1/2}$ = 128 min) evidence that spontaneous fragmentation of iodonium azide **3a** delivers ca. 10% **5a** within the first 10 min. By this time, the CuOTf-catalyzed conversion of **3a** to azide **4a** in CH_2Cl_2 is almost 90%.[22] Consequently, the regioselectivity of the Cu-catalyzed conversion of **3a** to **4a** is

Table 3. Sequential One-Pot Synthesis of Heteroaryl Azides 4a–u and Triazoles 6a–u



entry	product	time	yield (%)[c]	entry	product	time	yield (%)[c]
1	 **6a**	30 min	90	11	 **6k**	10 min	65
2	 **6b**	18 h	71	12	 **6l**	30 min	65
3	 **6c**	5 min	65	13	 **6m**	30 min	73
4	 **6d**	3 h	71	14	 **6n**	5 min	59
5	 **6e**	3 h	75	15	 **6o**	30 min	75
6	 **6f**	3 h	73	16	 **6p**[a]	30 min	62
7	 **6g**	18 h	72	17	 **6r**	5 min	70
8	 **6h**	10 min	64	18	 **6s**	72 h[b]	42
9	 **6i**	5 min	53	19	 **6t**	10 min	47
10	 **6j**	5 min	55	20	 **6u**	18 h	65

[a]DAGlc (diacetone-D-glucose). [b]A 2.2 equiv amount of TsOH–H_2O. [c]Yields were calculated on the basis of the starting heterocycle **1a–u**.

compromised by the competing noncatalyzed fragmentation to **5a**, and this observation renders CH_2Cl_2 inferior as a solvent compared to alternatives such as MeCN and DMSO (entry 2 vs entries 1 and 3, Table 2). The noncatalyzed fragmentation of **3a** in MeCN is considerably less pronounced, and azide **3a** is virtually stable in DMSO. Therefore, MeCN and DMSO are solvents of choice for CuCl-catalyzed fragmentation of iodonium azides (entries 13–15, Table 2).

The formed indolyl azide **4a** decomposed during attempted purification; however, it can be employed in further transformations without isolation. Thus, addition of substituted acetylene directly to azide **4a** and CuCl in the presence of DIPEA and AcOH[23] resulted in the clean formation of 1,4-disubstituted 1,2,3-triazole **6a** as a sole regioisomer.[24] Hence, CuCl catalyzed both the in situ formation of indolyl azide **4a** and its subsequent 1,3-dipolar cycloaddition with (3-chlorophenyl)acetylene (Table 3).[9]

A series of heterocycles was subsequently subjected to an azidation−cycloaddition sequence to show the scope of the developed methodology. All heterocycles that can form iodonium salts in the reaction with a mixture of $PhI(OAc)_2$ and TsOH are suitable substrates,[25] including indoles[26] **1a−g**, pyrroles[27] **1h−n**, thieno[3,2-*b*]pyrrole **1o**, pyrrolo[2,3-*b*]-pyridines **1p,r**, pyrrolo[3,2-*b*]pyridine **1s**, pyrrolo[2,3-*d*]-pyrimidine **1t**, and uracil[28] **1u** (Table 3). In general, the regioselectivity of heteroaryliodonium salt formation is consistent with that of S_EAr reactions. Thus, λ^3-iodanes are formed at the *β*-position of indoles **1a−g** and fused pyrroles **1o−t** at the *α*-position of pyrroles **1i,j,n** and at the fifth position of uracil **1u** (Table 3). In 2,5-disubstituted pyrroles **1h,k−m**, however, iodonium salts were formed at the *β*-position. Importantly, the reaction conditions are compatible with the presence of iodine, bromine, and chlorine, thus rendering feasible their further functionalization. *N*-Alkyl, *N*-aryl, *N*-benzoyl, and *N*-benzyl substituents as well as *N*-SEM protecting groups are tolerated (Table 3).

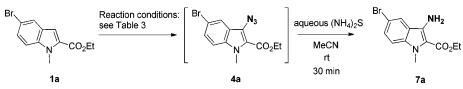
The formed heteroaryl azides **4a−u** could also be converted to the corresponding heteroaromatic amines **7a−u** by the in situ reduction with aqueous $(NH_4)_2S$ at room temperature within 30 min (see Table 4). Other reducing agents such as Ph_3P are equally efficient; however, the use of $(NH_4)_2S$ in the reduction generates less waste, requiring simple extractive workup to obtain crude products **7a−u**. In general, the one-pot three-step azidation−reduction sequence allows for amination of heteroaryl C−H bonds under mild conditions and in high overall yields.

Additional experiments have been carried out to determine the oxidation state of copper species responsible for the catalytic azidation of heterocycles. The considerably faster formation of **4a** in the presence of Cu(I) ions compared to Cu(II) counterparts (entry 7 vs entry 6, Table 2) suggests that Cu(I) salts are catalytically active species. This assumption was supported by the inhibition of **4a** formation by neocuproin (2 equiv with respect to CuOTf; see Figure 2). Neocuproin, a highly specific chelating agent for Cu(I) ions, forms a stable bright orange-colored complex of formula $Cu^I(neocuproin)_2$,[29] thus acting as an inhibitor of Cu(I)-catalyzed reactions.[30]

Kinetic studies demonstrated that the CuOTf-catalyzed conversion of **3a** to **4a** in DMSO-d_6 is first-order in CuOTf in the range of 0.25−5 mol % at 25 °C (Figure 3). This indicates that Cu(I) salts are involved in the rate-limiting step of the catalytic cycle. The decomposition of **3a** to **4a** was found to be zeroth-order with respect to the N_3 anion (Figure 4), suggesting that the formation of azide **4a** presumably is an intramolecular process. Finally, a radical inhibition test was also performed to verify the possibility of **3a** fragmentation via the radical chain pathway. Accordingly, the addition of radical scavengers such as 1,1-diphenylethylene[31] and 2,6-di-*tert*-butyl-4-methylphenol[6a] (both 200 mol % with respect to Cu(I)) did not affect the rate of CuOTf-catalyzed **3a** to **4a** conversion in CH_2Cl_2-d_2. Furthermore, we did not observe indole **1a**, which could form by a proton abstraction from solvent by indolyl radical during the decomposition of **3a**. All these data point against the involvement of free radical intermediates.[32]

A working mechanism for the Cu-catalyzed formation of heteroaryl azides is outlined in Scheme 1. Oxidative addition of iodonium azide **I** to Cu(I) salts would generate Cu(III) species **II**.[33] Complex **II** can directly collapse into azide **III** via the highly regioselective coupling of the heterocycle with the azide,

Table 4. Sequential Azidation−Reduction Sequence for One-Pot Synthesis of Heteroarylamines 7a−u



entry	product	yield (%)[a]
1	 **7a**	84
2	 **7b**	80
3	 **7d**	82
4	 **7f**	84
5	 **7g**	79
6	 **7h**	65
7	 **7j**	60
8	 **7k**	62
9	 **7m**	72
10	 **7n**	53
11	 **7o**	66
12	 **7p**	75
13	 **7u**	50

[a]Yields were calculated on the basis of the starting heterocycle **1a−u**.

and the regioselectivity of azide attack presumably is ensured by the formation of a transient *π*-complex between the highly electrophilic Cu(III) species and electron-rich heterocycle.[34] Alternatively, complex **II** can undergo regioselective transformation to PhI and heteroarylcopper(III) species **IV**,[35] followed by reductive elimination of **III** and regeneration of Cu(I) species.

To verify the role of putative *π*-Cu(III) complex **II** in the control of the regioselectivity of azide formation, we envisioned the in situ preparation of a *π*-complex between a suitable *π*-acidic transition metal and electron-rich heterocycle moiety of unsymmetrical λ^3-iodane **3a**. Among various transition metals, Os(II) species are known to form well-defined and stable η^2-complexes with pyrroles.[36] We examined the fragmentation of iodonium azide **3a** in the presence of 10 mol % Os-

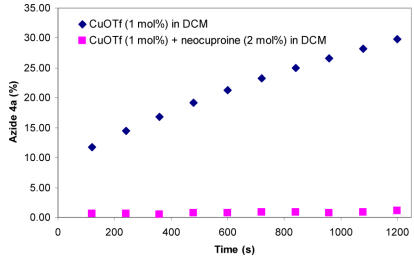


Figure 2. Inhibition of the CuOTf-catalyzed **3a** to **4a** conversion by neocuproin.

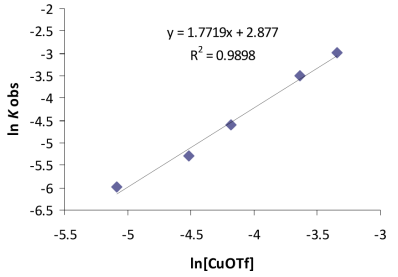


Figure 3. Initial rates vs concentration of CuOTf in DMSO-d_6.

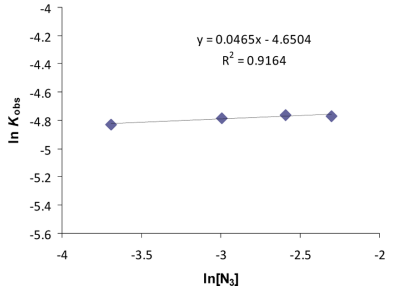


Figure 4. Initial rates vs concentration of azide ion in DMSO-d_6.

$[NH_3]_5(OTf)_3$ in CH_2Cl_2. Notably, indolyl azide **4a** was formed regioselectively (**4a**:**5a** = 7:3) within 30 min as a major product (30% conversion). This result is in sharp contrast to the opposite regioselectivity in the noncatalyzed decomposition of **3a** to **5a** in the presence of representative Lewis acids (entries 4, 5, and 17−19, Table 2). Possibly, π-complexation of a pyrrole ring to the Os(III) facilitates the substitution of the iodonium group by an azide nucleophile in transient complex **V** (Scheme 1); however, additional experiments are needed to support such a scenario.[37,38] The involvement of Cu(I) complex **V** (M = Cu(I)) to activate the heterocycle toward azide attack seems less likely because of insufficient electrophilicity of the Cu(I) species. Finally, Lewis acid activation of hypervalent iodonium species by Cu(I) or Cu(III) salts was shown to be kinetically insensitive to the concentration of copper species,[6a] an observation that contradicts our results.

CONCLUSIONS

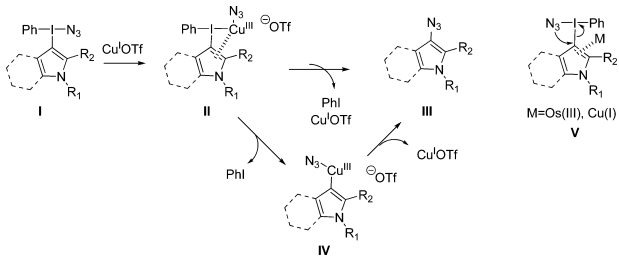
In summary, a rapid and versatile approach to heteroaryl azides via C−H to C−N bond transformation has been developed. The one-pot sequential procedure comprises formation of heteroaryl(phenyl)iodonium azides, followed by Cu(I)-catalyzed fragmentation to heteroaryl azides. The regioselectivity of the fragmentation is controlled by Cu(I) salts. The formed heteroaryl azides can be in situ reduced to heteroarylamines. Alternatively, the heteroaryl azides can undergo Cu-catalyzed click chemistry with a range of acetylenes to furnish 1,2,3-triazoles. The developed procedure is suitable for a variety of electron-rich heterocycles such as pyrroles, indoles, thienopyrroles, pyrrolopyridines, pyrrolopyrimidines, and uracil. Further studies to expand the scope of nucleophiles in the Cu-catalyzed regioselective fragmentation of heteroaryl(phenyl)iodonium salts are ongoing in our laboratory.

EXPERIMENTAL SECTION

Preparation of Iodonium Azides 3a and 3h. *Caution: Azides **3a,h** are thermally unstable and possess high thermal hazard potential.*[39] *Therefore, care must be taken during handling of azides **3a,h**, and a small scale is strongly encouraged.*

Ethyl 3-[(Azido)(phenyl)-λ^3-iodanyl]-1,5-dimethyl-1*H*-indole-2-carboxylate (3a). To a solution of $PhI(OAc)_2$ (509 mg, 1.58 mmol, 1.05 equiv) in CH_2Cl_2 (10 mL) was added $TsOH{\cdot}H_2O$ (342 mg, 1.80 mmol, 1.2 equiv), and the resulting suspension was stirred for 5 min at room temperature. Then a solution of indole **1a** (423 mg, 1.50 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added rapidly to the stirred suspension. The progress of the reaction was monitored by TLC, and within 30 min complete conversion of the starting **1a** was observed. The reaction was then poured into a solution of NaN_3 (146

Scheme 1. Working Mechanism for Azidation of Heterocycles



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mg, 2.25 mmol, 1.5 equiv) in water (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). Organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The solid residue was washed with diethyl ether to afford **3a** as a white powder (727 mg, 92% yield): analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, R_f = 0.56. Pure material was obtained by crystallization from CH_2Cl_2/diethyl ether: mp 102−103 °C dec; IR (film, cm^{-1}) 1999 (N═N═N), 1716 (C═O); ^1H NMR (400 MHz, DMSO-d_6, ppm) δ 8.13−8.07 (3H, m), 7.73 (1H, d, J = 9.0 Hz), 7.60 (1H, dd, J = 9.0, 1.6 Hz), 7.55−7.50 (1H, m), 7.45−7.40 (2H, m), 4.51 (2H, q, J = 7.1 Hz), 4.07 (3H, s), 1.43 (3H, t, J = 7.1 Hz); ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 159.1, 137.0, 133.9, 131.3, 131.2, 131.0, 129.1, 128.6, 123.5, 115.9, 114.6, 62.4, 33.5, 14.0; HRMS-ESI (m/z) calcd for $C_{18}H_{16}NO_2BrI$ $[M - N_3]^+$ 483.9409, found 483.9419.

Methyl 4-[(Azido)(phenyl)-λ^3-iodanyl]-1-(2-bromobenzyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (3h). The same procedure was used as for **3a**. Accordingly, 3-[1-(2-bromobenzyl)-4-(methoxycarbonyl)-2,5-dimethyl-1*H*-pyrrole (**1h**; 482 mg, 1.50 mmol) was converted to iodonium azide **3h**. Purification of the crude **3h** by washing with diethyl ether afforded product as a white powder (723 mg, 85% yield): analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, R_f = 0.54. Pure material was obtained by crystallization from CH_2Cl_2/diethyl ether: mp 96−97 °C dec; IR (film, cm^{-1}) 2002 (N═N═N), 1696 (C═O); ^1H NMR (400 MHz, DMSO-d_6, ppm) δ 7.95−7.91 (2H, m), 7.73−7.68 (1H, m), 7.61−7.55 (1H, m), 7.50−7.45 (2H, m), 7.29−7.24 (2H, m), 6.19−6.14 (1H, m), 5.30 (2H, s), 3.80 (3H, s), 2.43 (3H, s), 2.37 (3H, s); ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 162.3, 138.2, 137.5, 134.9, 133.5, 133.0, 131.2, 131.0, 129.7, 128.4, 126.1, 121.1, 110.4, 109.6, 51.3, 48.5, 12.6, 11.8; HRMS-ESI (m/z) calcd for $C_{21}H_{20}NO_2BrI$ $[M - N_3]^+$ 523.9722, found 523.9734.

Experimental Procedures for Substituted 1,2,3-Triazoles 6a−u. To a solution of $PhI(OAc)_2$ (0.53 mmol, 1.05 equiv) in MeCN (1.5 mL) was added TsOH·H_2O (0.60 mmol, 1.2 equiv), and the resulting suspension was stirred for 5 min at room temperature. Then a solution of heterocycle **1a−u** (0.50 mmol, 1 equiv) in MeCN (1 mL) was added to the stirred suspension, and the progress of the reaction was monitored by TLC (disappearance of the starting material spot; mobile phase petroleum ether:EtOAc = 3:1; the formed heteroaryliodonium salt does not migrate from the application point). Immediately upon full conversion of the starting **1a−u** (see Table 3 for the appropriate time), a solution of NaN_3 (0.75 mmol, 1.5 equiv) in water (500 μL) was added (*decomposition of the formed iodonium salt begins if the addition of NaN_3 is delayed*), followed by DMSO (2.5 mL) and solid CuCl (5 mg, 10 mol %; *CuCl must be added immediately after NaN_3 to avoid the noncatalyzed decomposition of iodonium azide*), whereupon the color of the reaction mixture changed to brown. After the reaction mixture was stirred for 30 min at room temperature, acetylene (0.75 mmol, 1.5 equiv), DIPEA (1.00 mmol, 2 equiv), and AcOH (1.00 mmol, 2 equiv) were added, and stirring was continued for 3 h at room temperature. The reaction mixture was poured into 50 mL of water and 25 mL of saturated $NaHCO_3$ and extracted with DCM (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel.

Experimental Procedures for Heteroarylamines 7a−u. To a solution of $PhI(OAc)_2$ (0.53 mmol, 1.05 equiv) in MeCN (4 mL) was added TsOH·H_2O (0.60 mmol, 1.2 equiv), and the resulting suspension was stirred for 5 min at room temperature. Then a solution of heterocycle **1a−u** (0.50 mmol, 1 equiv) in MeCN (1 mL) was added to the stirred suspension, and the progress of the reaction was monitored by TLC (disappearance of the starting material spot; mobile phase petroleum ether:EtOAc = 3:1; the formed heteroaryliodonium salt does not migrate from the application point). Immediately upon full conversion of the starting **1a−u** (see Table 3 for the appropriate time), a solution of NaN_3 (0.75 mmol, 1.5 equiv) in water (500 μL) was added (*decomposition of the formed iodonium salt begins if the addition of NaN_3 is delayed*), followed by solid CuCl (5 mg, 10 mol %; *CuCl must be added immediately after NaN_3 to avoid the noncatalyzed decomposition of iodonium azide*), whereupon the color of the reaction mixture changed to brown. After the reaction mixture was stirred for 30 min at room temperature, aqueous $(NH_4)_2S$ (40−48 wt % solution in water, Aldrich, 1.25 mmol, 200 μL, 2.5 equiv) was added. After being stirring for another 30 min at room temperature, the reaction mixture was poured into a mixture of water (50 mL) and saturated aqueous $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterization data, ^1H and ^{13}C NMR spectra, X-ray crystallographic data for iodonium azides **3a** and **3h** (CIF), and details of the kinetic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(38) Control experiments supported the importance of electronic effects in the regiocontrol of the Cu-catalyzed fragmentation of iodonium azide **3a**. Thus, replacement of the Ph group in **3a** with an electron-poor 4-$NO_2C_6H_4$ moiety altered the regioselectivity of azide attack and favored the formation of aryl azide 4-$NO_2C_6H_4N_3$ (**4a**:**5a** = 1:1 in MeCN and **4a**:**5a** = 1:3 in DCM). In the meantime, substitution of the Ph ring with a more electron-rich mesityl moiety in **3a** did not change the fragmentation regioselectivity (**4a**:**5a** = 9:1 in MeCN). Likewise, CuOTf-catalyzed decomposition of **3a** possessing a 4-$MeOC_6H_4$ moiety instead of a Ph ring afforded **4a**, albeit with diminished regioselectivity (**4a**:**5a** = 4:1 in DCM).

(39) The decomposition of indolyl azide **3a** was investigated by differential scanning calorimetry (DSC) and thermogravimetry methods. The DSC analysis of **3a** (heating rate 5 K/min) showed two exotherms: from 100 to 120 °C with a heat release of 122.0 J/g and from 212 to 263 °C with a heat release of 1842.7 J/g. The total decomposition enthalpy of 1964.7 J/g points toward a high thermal hazard potential for iodonium azide **3a**.

III

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Copper-Catalyzed Intermolecular C−H Amination of (Hetero)arenes via Transient Unsymmetrical λ^3-Iodanes

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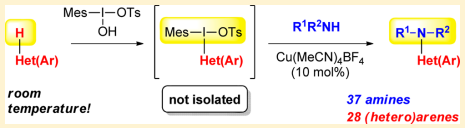
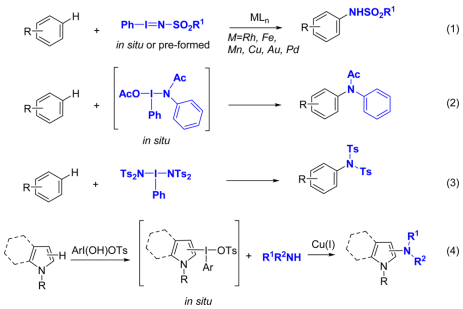
Supporting Information

ABSTRACT: A one-pot two-step method for intermolecular C−H amination of electron-rich heteroarenes and arenes has been developed. The approach is based on a room-temperature copper-catalyzed regioselective reaction of the in situ formed unsymmetrical (hetero)aryl-λ^3-iodanes with a wide range of primary and secondary aliphatic amines and anilines.



INTRODUCTION

Hypervalent iodine(III) species possessing an iodine−nitrogen bond are efficient reagents in oxidative C−H amination of nonprefunctionalized arenes and heteroarenes.[1] The most widely used are preformed or in situ generated sulfonylimino-λ^3-iodanes, which effect C−H to C−N bond transformations in the presence of transition metal catalyst (eq 1).[2] Phenyl-λ^3-



iodane (formed in situ from $PhI(OAc)_2$ and *N*-acetanilide) has been proposed as a precursor of acylnitrenium species in a transition metal-free C−H amination of arenes (eq 2).[3−5] Analogous phenyl-λ^3-iodanes possessing an iodine−nitrogen bond have also been suggested as plausible intermediates in an oxidative transfer of the phthalimide moiety to arene rings.[6,7] Recently, a well-defined bis-tosylimido-λ^3-iodane has been introduced by Muñiz for a metal-free oxidative amination of arenes and heteroarenes (eq 3).[8] All of the above-mentioned approaches, however, have a serious limitation: only amides, imides, and sulfonamides can be transferred to arenes or heteroarenes by hypervalent iodine(III) species. Simple amines are not compatible with these C−H amination conditions, as they are oxidized by monoaryl-λ^3-iodane reagents.[9] In contrast, amines are oxidatively stable toward diaryl-λ^3-iodanes, and these hypervalent iodine(III) species have been used for the *N*-arylation of amines.[10] Symmetrical diaryl-λ^3-iodanes are preferred for *N*-arylation because unsymmetrical diaryl-λ^3-iodanes usually form a mixture of *N*-arylation products.[10d,e]

We envisioned that a versatile method for C−H amination of (hetero)arenes with unprotected amines as the source of nitrogen could be developed, provided that the issue of regioselectivity of amine transfer to the desired aromatic ring of the unsymmetrical diaryl-λ^3-iodanes could be solved. Recently, we reported that a Cu(I) catalyst ensures complete regiocontrol in a reaction of azides with unsymmetrical diaryl-λ^3-iodanes.[11] During this study, it became evident that nucleophiles other than azide could be reacted regioselectively with a variety of unsymmetrical heteroaryl-λ^3-iodanes that are generated as intermediates using suitable ArI(OH)OTs reagent. Herein, we report a mild and versatile Cu(I)-catalyzed method for intermolecular C−H amination of electron-rich heterocycles (pyrroles, pyrrolopyridines, thienopyrroles, pyrrolopyrimidines, and uracil) as well as simple arenes, comprising a one-pot two-step room-temperature reaction between the (hetero)aryl-λ^3-iodanes formed in situ and a wide range of primary and secondary amines (eq 4). The reactivity pattern of the developed C−H amination approach is consistent with that of an electrophilic aromatic substitution (S_EAr) reaction. Because of the operational simplicity, mild reaction conditions, and wide substrate scope, our C−H amination approach provides a convenient way for C−H functionalization of heteroarenes,[12] a topic of high importance in medicinal and pharmaceutical chemistry given the drug-like properties of heteroarenes and abundance of heterocycles in drugs.

RESULTS AND DISCUSSION

At the outset of our investigation, we synthesized the indolyliodonium tosylate **2a** in a pure form from MesI(OH)-OTs[13] and indole **1a**. The structure of **2a** was confirmed by X-ray crystallographic analysis (Figure 1). λ^3-Iodane **2a** is stable in MeCN, DCM, and DMSO solutions at room temperature for

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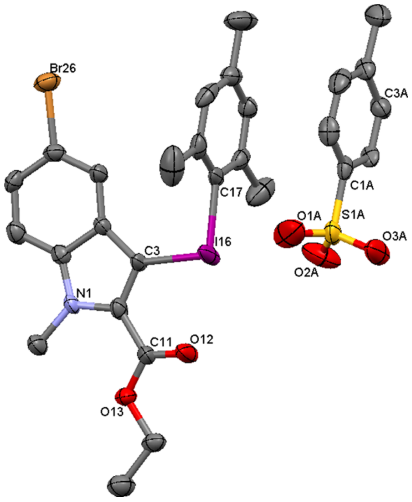


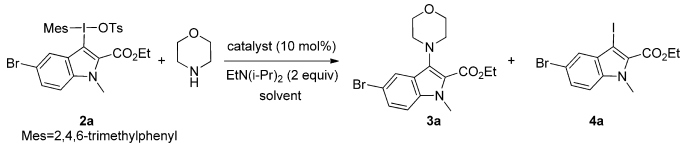
Figure 1. X-ray crystal structure of λ^3-iodane **2a** (ellipsoids at 50% probability) with hydrogen atoms omitted for clarity. Selected bond distances (Å) and angles (deg): I16−C3, 2.086(7); I16−C17, 2.108(8); I16−O12, 2.713(7); I−O1A, 3.088(9); I−O2A, 3.001(8); C3−I16−C17, 98.2(3). See the Supporting Information for details.

at least 72 h, but addition of morpholine and DIPEA to a DCM solution of **2a** brought about its slow transformation to iodoindole **4a** (entry 1, Table 1). The process was facilitated by using DMSO as solvent (entry 2). The conversion of **2a** to **4a** was highly selective, and only traces of indolylamine **3a** were observed. In striking contrast, addition of CuOTf (10 mol %) resulted in complete reversal of selectivity favoring the formation of the desired **3a**. Furthermore, the copper catalyst considerably decreased the reaction time (entry 3 vs entries 1−2, Table 1). Both Cu(I) and Cu(II) salts could be utilized; however, the Cu(I) species ensured faster reaction (entry 3 vs 4). Faster formation of **3a** helped to improve the **3a**:**4a** ratio by diminishing an impact of the competing noncatalyzed background formation of **4a** (entry 2). The determined initial rates of the noncatalyzed background reaction of **2a** with morpholine in DMSO (initial rate coefficient $k_{obs} = 1.98 \times 10^{-7}$ mmol mL^{-1} s^{-1}, DMSO-d_6, 25 °C) evidence that the background reaction delivers ca. 10% of **4a** within 90 min. By this time, the Cu(I)-catalyzed conversion of **2a** to **3a** is almost quantitative, so the faster is **3a** formation, the higher is **3a**:**4a** selectivity. Screening of various Cu(I) sources helped to identify the relatively stable $Cu(MeCN)_4BF_4$ as the most efficient catalyst (entry 5). λ^3-Iodane **2a**′ containing a Ph ligand instead of the mesityl group could also be used at the expense of slightly diminished selectivity (entry 6). However, Pd(II), Ni(II), and Sc(III) salts were inefficient as catalysts (entries 7−9, Table 1).[14]

Indolylamine **3a** could also be synthesized in a sequential one-pot approach without isolation of the iodonium salt **2a**. Accordingly, $Cu(MeCN)_4BF_4$, morpholine, and EtN(*i*-Pr)$_2$ were added to the reaction mixture after the corresponding λ^3-iodane **2a** had been formed.[15] The one-pot sequential C−H amination approach afforded lower yields of **3a** as compared to the two-step synthesis (74% vs 85%), but avoided the isolation and handling of potentially unstable intermediate λ^3-iodanes. This advantage compensates for the decreased yields.

Various amines were subsequently examined in the Cu(I)-catalyzed two-step one-pot C−H amination of indole **1a** (Table 2). A wide variety of aliphatic secondary amines (entries 1−11), aliphatic primary amines (entries 12−26), primary and secondary aromatic amines (entries 27−35), as well as a heteroarylamine (entry 36) and ammonia (entry 37) could be employed. Importantly, the reaction conditions are compatible with alkene and alkyne moieties in the amine (entries 10, 22, 23).[16] *N*-Boc (entry 17), *N*-acetyl (entry 5), and *S*-trityl (entry 20) protecting groups, acetals (entry 21), ketals (entry 2), as well as various functional groups such as esters (entry 30), nitriles (entries 9,15), nitro (entry 31), and halides (entries 24, 25, 28) are all tolerated. Sterically hindered amines (entries 14,

Table 1. Reaction of λ^3-Iodane 2a with Morpholine



2a
Mes=2,4,6-trimethylphenyl

3a **4a**

entry	catalyst (10 mol %)	solvent, time	conversion %[a,b]	**3a**:**4a** ratio, (yield %)[b,c]
1	none	CH_2Cl_2, 24 h	15	1:99 (8)
2	none	DMSO, 24 h	81	1:99 (67)
3	CuOTf·PhH	CH_2Cl_2−DMSO 4:1, 1.5 h	60	97:3 (46)
4	$Cu(OTf)_2$	CH_2Cl_2−DMSO 4:1, 1.5 h	22	93:7 (14)
5	$Cu(MeCN)_4BF_4$	CH_2Cl_2−DMSO 4:1, 1 h	92	97:3 (85)[d]
6[e]	$Cu(MeCN)_4BF_4$	CH_2Cl_2-DMSO 4:1, 1.5 h	93	89:11 (76)
7	$Pd(OCOCF_3)_2$	CH_2Cl_2−DMSO 4:1, 1.5 h	5	1:99 (3)
8	$Ni(OTf)_2$	CH_2Cl_2−DMSO 4:1, 1.5 h	5	1:99 (5)
9	$Sc(OTf)_3$	CH_2Cl_2−DMSO 4:1, 1.5 h	7	1:99 (5)

[a]Conditions: λ^3-iodane **2a** (1.0 equiv), morpholine (1.2 equiv), solvent (10 mL/1 mmol of **2a**), room temperature. [b]Determined by LC−MS assay. [c]Yield of the major product. [d]Isolated yield of >95% pure indole **3a**. [e]λ^3-Iodane **2a**′ possessing Ph ligand instead of a mesityl group (Mes = Ph) was used.

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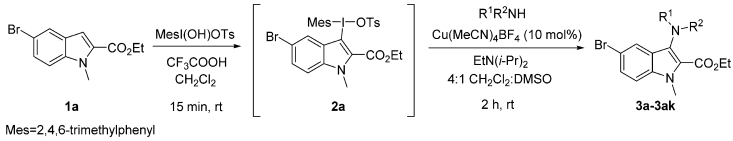
Table 2. Sequential One-Pot Synthesis of Indolylamines 3a−3ak[a]



entry	R^1R^2NH	Yield (%)	entry	R^1R^2NH	Yield (%)	entry	R^1R^2NH	Yield (%)
1		**3a**, 74	14		**3n**, 76	26		**3z**, 79
2		**3b**, 66	15		**3o**, 63	27		**3aa**, 73
3		**3c**, 75	16		**3p**, 67	28		**3ab**, 74
4		**3d**, 71	17		**3q**, 73	29		**3ac**, 54
5		**3e**, 76	18		**3r** ,40	30		**3ad**, 69
6		**3f**, 76	19		**3s**, 75	31		**3ae**, 67
7		**3g**, 70	20		**3t**, 73	32		**3af**, 62
8		**3h**, 35[b]	21		**3u**, 80	33		**3ag**, 79
9		**3i**, 65	22		**3v**, 80	34		**3ah**, 76
10		**3j**, 67	23		**3w**, 71	35		**3ai**, 77
11		**3k**, 65	24		**3x**, 83	36		**3aj**, 65
12		**3l**, 71	25		**3y**, 77	37		**3ak**, 71[c]
13		**3m**, 70						

[a]Conditions: Indole **1a** (1.0 equiv), MesI(OH)OTs (1.1 equiv), CF_3COOH (1.2 equiv), CH_2Cl_2 (4 mL/1 mmol of **1a**), room temperature, 15 min; then amine (1.2 equiv), EtN(*i*-Pr)$_2$ (2.0 equiv), $Cu(MeCN)_4BF_4$ (0.1 equiv), 1:1 CH_2Cl_2:DMSO (4 mL/1 mmol of **1a**), room temperature, 2 h. [b]Reaction time for the formation of **3h** from λ^3-iodane: 18 h. [c]3 equiv of EtN(*i*-Pr)$_2$ was used.

33, 34) are also suitable as substrates.[17] Amines react chemoselectively in the presence of unprotected alcohol (entry 16), amide (entry 6), and sulfonamide moieties (entry 32), and monoamination with piperazine is also possible (entry 7). It should be noted that moderate yields were obtained for bi- and tridentate amines potentially capable of chelating the Cu(I) catalyst (entries 8, 18).

Next, the scope of substrates for the C−H amination was surveyed employing morpholine, cyclopropylmethylamine, and 4-bromoaniline as representative amines (Table 3). All heterocycles that react with MesI(OH)OTs and form iodonium salts that survive in solution are suitable as substrates, including 2-substituted indoles (entries 1−6),[18] pyrroles (7−14), thieno[3,2-*b*]pyrrole (entries 15, 16), pyrrolo[2,3-*b*]pyridines (entries 17, 18), pyrrolo[2,3-*d*]pyrimidine (entry 19), pyrazoles (entries 20−22), and *N*,*N*-dimethyluracil (entry 23). The formation of the intermediate iodonium salts was found to be sensitive to the electronic properties of heterocycle.[19] Thus, relatively electron-rich *N*-alkyl pyrroles (entries 7−10, 12−14) and pyrrolo[2,3-*b*]pyridine (entry 18) reacted rapidly and produced the intermediate iodonium salts within 5 min. In contrast, introduction of an electron-withdrawing *N*-acyl moiety in pyrrole (entry 11) increased the reaction time to 30 min. The formation of iodonium salts from less electron-rich heterocycles such as indoles (entries 1−6), pyrrolo[2,3-*b*]pyridine (entry 17), pyrrolo[2,3-*d*]pyrimidine (entry 19), pyrazoles (entries 20−22), and *N*,*N*-dimethyluracil (entry 23) was considerably slower. However, the reaction of these substrates with MesI(OH)OTs could be facilitated by addition of CF_3COOH (1.2 equiv). This did not work always, and pyrroles possessing several electron-withdrawing substituents such as *N*-tosyl-1*H*-pyrrole-2-carboxylic acid ethyl ester did not give substantial conversion to the corresponding iodonium salt under our standard conditions with added CF_3COOH. Furthermore, potential substrates such as *N*-methylbenzimidazole, benzo[*b*]-thiophene, and ethyl thiophene-2-carboxylate were also unreactive. Apparently, the latter heterocycles are insufficiently electron-rich to produce iodonium salts in the reaction with MesI(OH)OTs. On the other hand, we were especially pleased to find that electron-rich carbocyclic arenes undergo C−H amination as exemplified in Table 4. Surprisingly, even the simple substrates such as tetraline (entry 1) and *N*-Boc-*N*-methylaniline (entry 2) could be employed in the C−H amination reaction. The formation of the intermediate diaryl-λ^3-iodane from tetraline (entry 1) required prolonged time (18 h) apparently because of insufficiently electron-rich nature of tetraline. The presence of electron-releasing alkoxy groups facilitates considerably the formation of intermediate diaryl-λ^3-iodane (entries 3−5 vs entry 1). Further improvement of C−H amination yields was achieved for arenes containing two electron-releasing substituents (entries 6−9, Table 4). In general, the more electron-rich is (hetero)arene, the shorter are the times required to produce the intermediate diaryl-λ^3-iodane. However, transient λ^3-iodanes formed from electron-rich (hetero)arenes usually are unstable and are prone to undesired decomposition if the addition of Cu catalyst and/or

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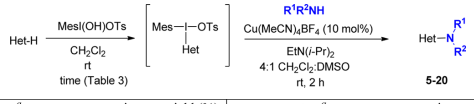
Table 3. C−H Amination of Heterocycles



entry	product[a]	time	yield (%)	entry	product[a]	time	yield (%)
1	 **5**	30 min[b]	69	13	 **13b**	5 min	71
2	 **6**	30 min[b]	79	14	 **13c**	5 min	65
3	 **7a**	18 h[b]	84	15	 **14b**	2 h	57
4	 **7b**	18 h[b]	77	16	 **14c**	2 h	62
5	 **8**	18 h[b]	50	17	 **15**	1 h[b]	78
6	 **9**	18 h[b]	72	18	 **16**	5 min[c]	62
7	 **10a**	5 min	70	19	 **17**	3 h[b]	60
8	 **10b**	5 min	62	20	 **18**	5 h[b]	52
9	 **11a**	5 min	60	21	 **19a**	24 h[b]	60
10	 **11b**	5 min	62	22	 **19b**	24 h[b]	62
11	 **12**	30 min	63				
12	 **13a**	5 min	91	23	 **20**	18 h[b]	65

[a]Conditions: Heteroarene (1.0 equiv), MesI(OH)OTs (1.1 equiv), CH_2Cl_2 (4 mL/1 mmol of the starting heteroarene), 15 min; then amine (1.2 equiv), EtN(*i*-Pr)$_2$ (2.0 equiv), Cu(MeCN)$_4$BF$_4$ (0.1 equiv), 2:1 CH_2Cl_2:DMSO (4 mL/1 mmol of the starting heteroarene), room temperature, 2 h. [b]In the presence of CF_3COOH (1.2 equiv). [c]λ^3-Iodane was formed at −20 °C.

amine is delayed. Therefore, it is important to establish the optimum conversion time of the starting (hetero)arene into λ^3-iodane.

The regioselectivity of the C−H amination is controlled at the stage of the formation of the intermediate iodonium salts. Although the regioselectivity is a result of the combined directing effects of substituents in heterocycles and arenes, in general, it is consistent with that of electrophilic aromatic substitution (S_EAr) reactions. Thus, λ^3-iodanes are formed at the β-position of indoles (entries 1−6, Table 3) and fused pyrroles (entries 15−19), at the α-position of pyrroles[20a] (entries 9, 10, 12−14), and at position 5 of uracil[20b] (entry 23), while 2,5-disubstituted pyrroles (entries 7, 8, 11) produce iodonium salts at the β-position. In the case of simple arenes, intermediate λ^3-iodanes are selectively formed in the *para*-position to the strongest electron-releasing substituent in the molecule, for example, alkyl moiety (entry 1, Table 4), *N*-Boc-*N*-methylamino group (entry 2), alkoxy (entry 4), and MeO groups (entries 3, 5−8).[21] Interestingly, C−H amination proceeds in *para*-position to the MeO group also in *N*-protected methoxyanilines (entries 9−11), substrates that possess two different electron-releasing substituents. The observed regioselectivity of C−H amination in *meta*-anisidines (entries 10, 11) might also be attributed to stabilization of intermediate λ^3-iodane by the adjacent *N*-Boc moiety. However, we regard such stabilization unlikely because *N*-Boc-*N*-methylaniline underwent C−H amination in the *para*-position, and not next to the aniline nitrogen (entry 2, Table 4). Notably, all of the other C−H amination products (Tables 3 and 4) were likewise obtained as pure regioisomers, and the formation of minor isomers was not observed within ^{1}H NMR detection limits.

The C−H amination conditions are compatible with the presence of *O*-allyl (entry 1, Table 3), *O*-*tert*-butyl (entry 2, Table 3), *O*-alkyl ester moieties (entries 5−10, 12−17, Table 3), as well as amides (entries 7, 8, Table 4) and *tert*-butyl carbamates (entries 2, 10, 11, Table 4). The successful C−H amination of substrates containing secondary amide (entry 7, Table 4) and carbamate (entry 10, Table 4) moieties is noteworthy, because structurally related *N*-acetanilides react with PhI(OAc)$_2$ and generate highly reactive acylnitrenium species.[3b,d] Bromine and chlorine substituents in the substrate

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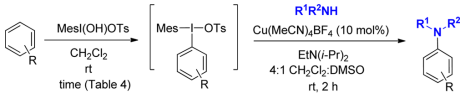
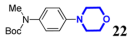
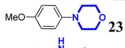
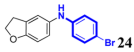
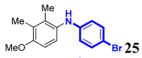
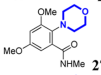
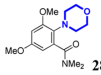
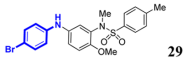
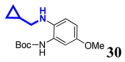
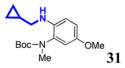
Table 4. C−H Amination of Arenes



21-31

entry	product[a]	time	yield (%)
1	 **21**	18 h[b]	41
2	 **22**	30 min[b]	30[c]
3	 **23**	30 min[b]	52
4	 **24**	30 min	49
5	 **25**	30 min[b]	56
6	 **26**	30 min[b]	61
7	 **27**	30 min[b]	71
8	 **28**	30 min[b]	74
9	 **29**	18 h[b]	60
10	 **30**	30 min	40
11	 **31**	60 min	50

[a]Conditions: Arene (1.0 equiv), MesI(OH)OTs (1.1 equiv), CH_2Cl_2 (4 mL/1 mmol of the starting arene), 15 min; then amine (1.2 equiv), EtN(*i*-Pr)$_2$ (2.0 equiv), Cu(MeCN)$_4$BF$_4$ (0.1 equiv), 2:1 CH_2Cl_2:DMSO (4 mL/1 mmol of the starting arene), room temperature, 2 h. [b]In the presence of CF_3COOH (1.2 equiv). [c]At 70% conversion.

as well as *N*-benzoyl, *N*-benzyl, *N*-tosyl, and *N*-SEM protecting groups are also tolerated (Tables 3 and 4).

Mechanistic Studies. Although both Cu(I) and Cu(II) salts can be employed as catalysts in the C−H amination reaction, the considerably faster formation of **3a** in the presence of Cu(I) species as compared to Cu(II) (entry 3 vs entry 4, Table 1) suggests that Cu(I) salts are the catalytically active species. The slow formation of **3a** in the Cu(II)-catalyzed reaction (entry 4, Table 1) could be ascribed to an in situ reduction of Cu(II) to active Cu(I) catalyst by amine.[22,23] To verify the catalytic efficiency of Cu(I) species, the Cu(OTf)$_2$-catalyzed C−H amination of **2a** was performed in the presence of 2 equiv of neocuproin, a highly specific chelating agent for Cu(I) ions. Neocuproin (2,9-dimethyl-1,10-phenanthroline) is a bidentate ligand that forms a stable bright orange-colored complex of formula Cu^{I}(neocuproin)$_2$,[24] thus acting as an inhibitor of Cu(I)-catalyzed reactions.[25] Complete inhibition of the Cu(OTf)$_2$-catalyzed formation of **3a** in the presence of neocuproin was observed, evidencing that the catalytically active species are indeed Cu(I) salts.

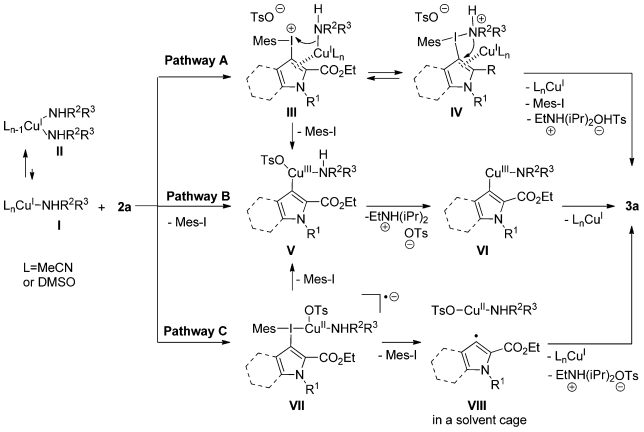
A radical inhibition test was performed to exclude the possibility of C−H amination of **2a** via a radical chain pathway. Accordingly, the addition of radical scavengers such as 2,6-di-*tert*-butyl-4-methylphenol (BHT)[26] and TEMPO[27] (both in 10-fold excess with respect to Cu(I)) did not affect the rate of Cu(MeCN)$_4$BF$_4$-catalyzed conversion of **2a** to **3a** in CH_2Cl_2−DMSO = 4:1. These data strongly argue against the involvement of a radical chain process. Notably, the addition of radical scavengers considerably decelerated the background noncatalyzed reaction of λ^3-iodane **2a** with morpholine to produce **4a** (Table 1, entry 2). Thus, only 27% of **4a** was formed in the presence of TEMPO after 24 h at room temperature (at 31% conversion of **2a**), and 15% of **4a** (at 24% conversion) was observed after 12 h at room temperature with added BHT (both radical scavengers were added in equimolar amounts to the starting **2a**). Presumably, the noncatalyzed reaction of λ^3-iodane **2a** with morpholine proceeds through a radical chain pathway.

Kinetic studies were also carried out to establish the kinetic order of Cu(I)-catalyzed C−H amination of **2a** in each reaction component. Morpholine was employed both as a nucleophile and as a base, and (CuOTf)$_2$·PhH was used as a catalyst. The reactions were monitored by NMR spectroscopy, and the method of initial rates was used to determine rate coefficients. The Cu(I)-catalyzed conversion of **2a** to **3a** in DMSO-d_6 at 25 °C was found to be first-order in (CuOTf)$_2$·PhH (see Supporting Information, Figure S2), first-order in morpholine (see Supporting Information, Figure S3), and zeroth-order in λ^3-iodane **2a** (see Supporting Information, Figure S4). These data indicate that the Cu(I) catalyst and morpholine are both involved in the rate-limiting step of the catalytic cycle, whereas the subsequent reactions of λ^3-iodane **2a** are fast. It is likely that (CuOTf)$_2$·PhH and morpholine form a complex **I**, which exists in equilibrium with the bis-amine complex **II**. Assuming that **II** is a resting state of the catalyst,[28] dissociation of morpholine under equilibrium conditions would produce a catalytically active complex **I** (Scheme 1).

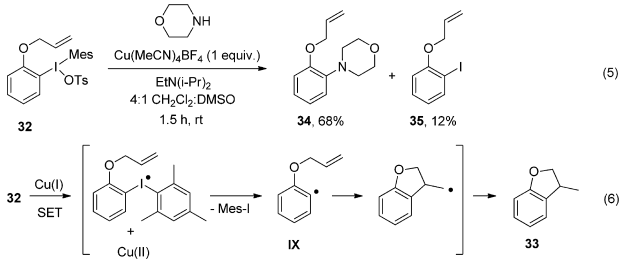
Several plausible pathways for Cu(MeCN)$_4$BF$_4$-catalyzed C−H amination of **2a** are consistent with the data above (Scheme 1). In pathway A, Cu(I)−amine complex **I** coordinates with the electron-rich indole moiety in the λ^3-iodane **2a**, forming a η^2-complex **III**. Subsequent substitution of tosylate by amine in the intermediate **III** and reductive elimination from the highly unstable λ^3-iodane **IV**[29] would lead to aminoheterocycle **3a**. The formation of η^2-coordinated species such as **III** and **IV** has been proposed in the transition state for the oxidative addition of aryl halides to Cu(I) complexes.[28a,30] π-Interaction between the Cu(I)−amine complex **I** and indole **2a** should increase electrophilicity of the heterocycle *ipso*-carbon in the putative intermediates **III** and **IV**, thus facilitating C−N bond forming reductive elimination from λ^3-iodane **IV**. However, other Lewis acids such as Pd(OCOCF$_3$)$_2$, Ni(OTf)$_2$, and Sc(OTf)$_3$ did not catalyze the formation of **3a** (Table 1, entries 7−9), so the involvement of η^2-coordination between Cu(I) species and the indole moiety in intermediates **III** or **IV** can be questioned.

In an alternative possibility, pathway B involves direct oxidative addition of the λ^3-iodane **2a** to Cu(I)−amine complex **I** to form the Cu(III) intermediate **V**.[31] For unsymmetrical diaryl-λ^3-iodanes, regioselectivity of the oxidative addition to Cu(I) species can be controlled by the use of a mesityl group as

Scheme 1. Plausible Pathways for C−H Amination of Heteroarenes



Scheme 2. C−H Amination of λ^3-Iodane 32 Containing a Radical Probe



a nontransferable aryl ligand.[31c−f,32] The Cu(III) intermediate **V** undergoes N−H deprotonation of the Cu(III)-coordinated amine with EtN(*i*-Pr)$_2$.[33] Product-forming reductive elimination from the resulting Cu(III)−amide complex **VI** would afford **3a** and regenerate a catalytically active Cu(I) species.[34] However, the proposed transient Cu(III) complexes **V** or **VI** could not be detected, presumably because they undergo rapid C−N bond forming reductive elimination.[35] This behavior is expected because related, highly reactive Cu(III) species have only been observed in chelation-stabilized complexes based on stabilizing triazamacrocyclic ligands.[36]

As a third option, pathway C involves a Cu(I)/Cu(II) catalytic cycle, which starts with an inner-sphere single-electron transfer (SET) from Cu(I)-complex[22,25b,37] to the λ^3-iodane **2a**, generating an intimate radical anion−Cu(II) complex **VII**.[38] Experimental redox potentials versus SCE were determined by cyclic voltammetry for λ^3-iodane **2a** (E = −0.76 V) and for Cu(MeCN)$_4$BF$_4$ (E = +0.85 V),[39] and they support the feasibility of SET between Cu(I) catalyst and iodonium salt **2a**. The radical anion−Cu(II) complex **VII** might undergo fragmentation to a radical pair **VIII**, which couples with the amine moiety with a second SET that regenerates the Cu(I) species.[40] To test for the intermediacy of heteroaryl radicals in the Cu(I)-catalyzed C−H amination reaction, diaryl-λ^3-iodane **32** containing an *O*-allyl moiety as a radical clock probe was employed as substrate in the reaction with morpholine in the presence of equimolar and catalytic (10 mol %, not shown) amounts of Cu(MeCN)$_4$BF$_4$ (Scheme 2, eq 5). It has been demonstrated that the λ^3-iodane **32**-derived aryl radical **IX** undergoes extremely rapid 5-*exo*-*trig* cyclization (rate constant k = 9.6 × 10^9 s^{-1}) to furnish 3-methyl-2,3-dihydrobenzofurane **33** after abstraction of the hydrogen atom from the medium (Scheme 2, eq 6).[41] In our hands, *N*-substituted morpholine **34** was obtained as the major product, and no detectable amount of the cyclization product **33** was observed (Scheme 2, eq 5).[42] These data provide strong evidence that the Cu(I)-catalyzed C−H amination occurs without involvement of free heteroaryl radicals such as **VIII** (Scheme 1, pathway C). On the other hand, the putative radical anion−Cu(II) complex **VII** may undergo a radical recombination to furnish aryl−Cu(III) species **V**.[43] The subsequent steps would involve the same conversion from **V** to **VI** as in pathway B. Although we regard the latter scenario as the most probable, neither pathway A nor pathway C could be ruled out. Further mechanistic studies are necessary to fully elucidate the mechanism of the newly developed C−H amination approach.

CONCLUSIONS

In summary, a versatile method for an intermolecular C−H amination of electron-rich heteroarenes and arenes has been

developed. The one-pot sequential two-step procedure comprises the in situ formation of unsymmetrical (hetero)-aryl-λ^3-iodanes followed by their Cu(I)-catalyzed reaction with a wide range of primary and secondary aliphatic amines and anilines. The Cu(I) catalyst ensures the desired selectivity in the reaction between the intermediate unsymmetrical λ^3-iodanes and amines. Initial mechanistic studies point toward a stepwise oxidative addition and involvement of single electron transfer from Cu(I) catalyst to unsymmetrical (hetero)aryl-λ^3-iodanes. The reaction proceeds at room temperature and tolerates a number of functional groups both in the amine and in the (hetero)arene. The regioselectivity of the C−H activation is typical for electrophilic aromatic substitution (S_EAr) reactions. Our C−H amination approach is an alternative and complementary method to transition metal-catalyzed direct intermolecular C_{sp2}−H amination of arenes,[44] which often requires the presence of a metalation-directing group in substrate[45] and employs imides, amides, sulfonamides, as well as organic azides or preactivated amino precursors such as *N*-chloroamines as sources of nitrogen.[46] In cases where the transition metal-catalyzed amination is not applicable, our method may be especially useful for late-stage amination of pharmaceutically relevant aromatics, and especially heterocycles.

EXPERIMENTAL SECTION

Ethyl 5-Bromo-1-methyl-3-({[(4-methylphenyl)sulfonyl]oxy}-(2,4,6-trimethylphenyl)-λ^3-iodanyl)-1*H*-indole-2-carboxylate (2a). To a solution of MesI(OH)OTs (2.39 g, 5.50 mmol, 1.1 equiv) in CH_2Cl_2 (10 mL) was added TsOH·H_2O (1.05 g, 5.50 mmol, 1.1 equiv), and the resulting suspension was stirred for 5 min at room temperature. Next, a solution of indole **1a** (1.41 g, 5.00 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added rapidly to the well-stirred suspension. The progress of the reaction was monitored by TLC (disappearance of the starting material spot, R_f = 0.55, 1:5 EtOAc/petroleum ether), and complete conversion of the starting **1a** was observed within 30 min. Solvent was concentrated to ca. 2/3 of the original volume, and Et_2O was added (50 mL). Formed precipitate was filtered, washed with Et_2O (100 mL), and dried in vacuo to afford **2a** as a white powder (3.30 g, 95% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, R_f = 0.49. Pure material was obtained by crystallization from CH_2Cl_2/diethyl ether: mp 125 °C. dec IR (film, cm^{-1}): 1710 (C═O), 1206 (SO_2). ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 7.79 (1H, d, J = 9.0 Hz), 7.61 (1H, dd, J = 9.0, 1.8 Hz), 7.48−7.43 (3H, m), 7.21−7.16 (2H, m), 7.10 (2H, d, J = 8.0 Hz), 4.45 (2H, q, J = 7.2 Hz), 4.08 (3H, s), 2.58 (6H, s), 2.28 (6H, s), 1.38 (3H, t, J = 7.2 Hz). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm): δ 159.4, 145.8, 142.9, 141.9, 137.5, 137.2, 131.8, 129.8, 128.1, 128.0, 125.5, 122.7, 121.7, 115.7, 115.1, 81.2, 62.8, 33.8, 26.1, 20.8, 20.4, 13.8. HRMS−ESI (m/z) calcd for $C_{21}H_{22}BrINO_2$ [M − OTs]$^+$ 525.9873, found 525.9861.

General Procedure for C−H Amination of Heterocycles and Arenes. To a solution of MesI(OH)OTs (239 mg, 0.55 mmol, 1.1 equiv) in anhydrous CH_2Cl_2 (1 mL) under argon atmosphere was added a solution of heterocycle or arene (0.50 mmol, 1 equiv) in anhydrous CH_2Cl_2 (1 mL). For a less reactive substrate (see Tables 3 and 4), neat TFA (46 μL, 0.60 mmol, 1.2 equiv) was then added slowly (dropwise, within 2−3 min; too fast addition of TFA leads to the formation of side-products). The resulting solution (color range: pale yellow to brown) was stirred at room temperature under argon atmosphere, and the progress of the reaction was monitored by TLC (disappearance of the starting material spot; mobile phase 3:1 light petroleum ether/EtOAc; the intermediate λ^3-iodane does not migrate from the application point). Immediately upon full conversion of the starting heterocycle or arene (see Tables 3 and 4 for appropriate time), the reaction mixture was transferred via cannula to another flask, which contained preweighed solid $Cu(MeCN)_4BF_4$ (16 mg, 0.05 mmol, 10 mol %) and a magnetic stirbar, and the source flask was rinsed with CH_2Cl_2 (1 mL). To the resulting well-stirred suspension was immediately added a solution of amine or aniline (0.6 mmol, 1.2 equiv) in anhydrous CH_2Cl_2 (1 mL) (Important: Decomposition of the formed λ^3-iodane begins if the addition of Cu catalyst and/or amine is delayed!). Finally, neat DIPEA (174 μL, 1.00 mmol, 2 equiv) was added, followed by DMSO (1 mL). The resulting solution was stirred at room temperature under argon atmosphere, and the progress of the reaction was monitored by TLC (the intermediate λ^3-iodanes have R_f = 0.4−0.6; mobile phase 20:80:5 MeOH/CH_2Cl_2/AcOH). In most cases, the reaction was completed in 2 h. The solution was poured into 50 mL of water and 20 mL of saturated aqueous ammonia solution, extracted with CH_2Cl_2 (3 × 30 mL), and combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterization data, ^1H and ^{13}C NMR spectra, X-ray crystallographic data for λ^3-iodane **2a** (CIF), cyclic voltammograms (CV), and details of the kinetic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) 2-Unsubstituted indoles as well as indoles possessing relatively electron-rich substituents such as 2-methyl or 2-phenyl groups form intermediate indolyl-λ^3-iodanes, which could be transformed into the corresponding indolyl-3-amines. However, the latter are unstable and undergo rapid oxidation under the C−H amination conditions. The low stability of indolyl-3-amines toward oxidation is well-known, see, for example: (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970; pp 290−291. (b) Huang-Hsinmin; Mann, F. G. *J. Chem. Soc.* **1949**, 2903. (c) Bruni, P.; Colonna, M.; Greci, L. *Tetrahedron* **1971**, *27*, 5893. Consequently, the presence of stabilizing electron-withdrawing substituents at position 2 of indole is necessary to obtain stable indolyl-3-amines.
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IV

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Copper-Catalyzed *para*-Selective C−H Amination of Electron-Rich Arenes

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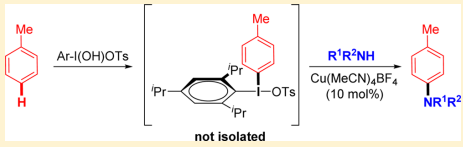
Supporting Information

ABSTRACT: A one-pot two-step method for *para*-selective C−H amination of carbocyclic arenes comprises the *in situ* formation of unsymmetrical diaryl-λ^3-iodanes followed by their Cu(I)-catalyzed reaction with a range of N-unprotected amines.

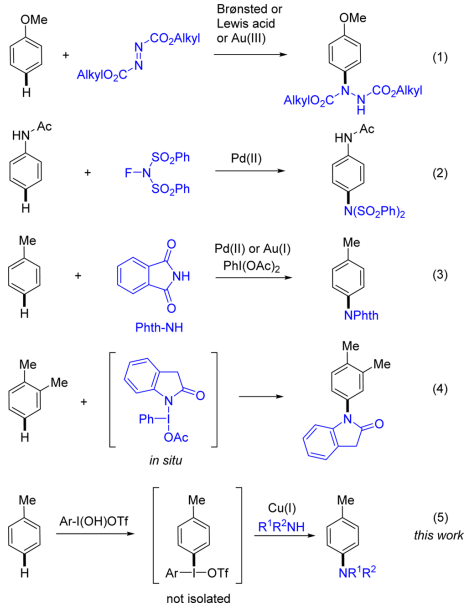


KEYWORDS: *hypervalent iodine, diaryliodonium salts, copper, amination, regioselectivity*

INTRODUCTION

Late-stage modification of pharmaceutically relevant compounds allows for introduction of a structural diversity at final stages of synthesis and provides rapid and straightforward access to a number of analogues. Therefore, late-stage modification is frequently employed to streamline the lead-optimization process in drug development.[1] Ideally, introduction of structural diversity is to be accomplished without preactivation of the lead compound. Hence, the most suitable approach to late-stage modification relies on the functionalization of C−H bonds.

Among a variety of C−H functionalization methods, the intermolecular C−H amination has become a focus of an increasing amount of research in recent years. Notwithstanding remarkable advances in the field of transition metal-catalyzed Csp^2−H amination,[2,3] a majority of the developed methods require the presence of a metal-coordinating substituent[4] that facilitates the cleavage of an *ortho*-C−H bond by a transition metal. Therefore, most of the reported catalytic C−H to C−N transformations in arenes are directed to the *ortho* position.[5] Recently, auxiliary substituents capable of directing C−H activation to the *meta*-position have been designed;[6] however, the directed *meta*-C−H amination has not been reported thus far. Likewise, a complementary *para*-selective Csp^2−H amination methodology is considerably less developed than directed *ortho*-C−H amination. Thus, there are a handful of *para*-selective Csp^2−H amination examples in the literature. Early reports describe electrophilic aromatic substitution of electron-rich arenes with azodicarboxylates in the presence of Lewis acids[7] or Brønsted acids[8] and, more recently, in a Au(III)-catalyzed process (eq 1).[9] Zhang has reported an amide-directed Pd-catalyzed *para*-C−H imidation with *N*-fluorobenzenesulfonimide (NFBS) as a source of nitrogen (eq 2).[10] High *para* selectivity levels of Csp^2−N bond formation in arenes have been achieved by using hypervalent iodine(III) reagents. Thus, $PhI(OAc)_2$-mediated oxidative transfer of a phthalimide moiety to arene rings proceeded



with reasonable *para* selectivity in the presence of a Au(I) catalyst (eq 3).[11] Relevant to our work is a transition metal-free *para*-C−H amidation of arenes in the presence of $PhI(OAc)_2$

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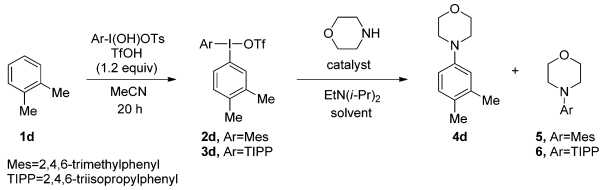
Table 1. Reaction of λ^3-Iodanes 2d and 3d with Morpholine



entry	λ^3-iodane	catalyst, mol %	solvent	time, temp	**4d** (%)[a,b]	**5**,%[b]	**6**,%[b]
1	**2d**	$Cu(MeCN)_4BF_4$, 10	CH_2Cl_2/DMSO, 4:1	8 days, rt	40	14	–
2	**2d**	$Cu(MeCN)_4BF_4$, 10	MeCN/DMSO, 1:4	8 days, rt	49	18	–
3	**3d**	$Cu(MeCN)_4BF_4$, 10	CH_2Cl_2/DMSO, 4:1	8 days, rt	39	–	<1
4	**3d**	$Cu(MeCN)_4BF_4$, 10	MeCN/DMSO, 1:4	12 h, 40 °C	80	–	<1
5	**3d**	$Cu(MeCN)_4BF_4$, 10	DMSO	12 h, 40 °C	83	–	<1
6	**3d**	$Cu(MeCN)_4BF_4$, 5	MeCN/DMSO, 1:4	40 h, 40 °C	84	–	<1
7	**3d**	$Cu(MeCN)_4BF_4$, 2	MeCN/DMSO, 1:4	48 h, 40 °C	75[c]	–	<1
8	**3d**	$Cu(MeCN)_4BF_4$, 0.5	MeCN/DMSO, 1:4	48 h, 40 °C	47[d]	–	<1
9	**3d**	CuI, 10	MeCN/DMSO, 1:4	24 h, 40 °C	75	–	<1
10	**3d**	$CuBr\cdot SMe_2$, 10	MeCN/DMSO, 1:4	130 h, 40 °C	37	–	<1
11	**3d**	CuOTf, 10	MeCN/DMSO, 1:4	130 h, 40 °C	26	–	<1
12	**3d**	$Cu(OTf)_2$, 10	MeCN/DMSO, 1:4	40 h, 40 °C	74[e]	–	<1
13	**3d**	$Cu(BF_4)_2\cdot 6H_2O$, 10	MeCN/DMSO, 1:4	60 h, 40 °C	31	–	<1
14[f]	**3d**	$Cu(MeCN)_4BF_4$, 10	MeCN/DMSO, 1:4	40 h, 40 °C	68	–	<1
15[g]	**3d**	$Cu(MeCN)_4BF_4$, 10	MeCN/DMSO, 1:4	40 h, 40 °C	67	–	<1
16	**3d**	none	MeCN/DMSO, 1:4	40 h, 40 °C	<1[h]	–	<1

[a]With 99% conversion of **2d** or **3d**. [b]Isolated yield of >95% pure product (NMR assay). [c]With 90% conversion of **3d**. [d]With 50% conversion of **3d**. [e]With 49% conversion of **3d** after 12 h at 40 °C. [f]In the presence of water (10 equiv). [g]Performed under air. [h]With 20% conversion of **3d**.

(eq 4), which presumably involves formation of a phenyl-λ^3-iodane intermediate possessing an iodine−nitrogen bond.[12] A single example of metal-free *para*-C−H imidation using bis-tosylimido-λ^3-iodane has recently been reported by Muñiz.[13] Importantly, in all of the examples mentioned above, additional synthetic steps are required to elaborate the C−H amination products into N-unsubstituted anilines. These postamination transformations reduce the synthetic advantages of the direct C−H to C−N transformation, so a method compatible with N-unprotected amines as the source of nitrogen would substantially increase the synthetic value of the *para*-selective Csp^2−H amination methodology.

In our continuing efforts to develop a synthetic method for the late-stage functionalization of pharmaceutically relevant heterocycles, we recently disclosed a Cu(I)-catalyzed Csp^2−H amination of heteroarenes with N-unprotected amines.[14] The one-pot two-step method comprised the reaction between arene and hypervalent iodonium reagent ArI(OH)OTs to form unsymmetrical diaryl-λ^3-iodanes, which reacted *in situ* with a range of N-unprotected amines in the presence of a Cu(I) catalyst to afford heteroarylamines. The developed method was suitable also for C−H amination of certain electron-rich carbocyclic arenes in moderate yields. Importantly, C−N bond formation in arenes proceeded in the *para* position with respect to electron-releasing substituents. Unfortunately, moderate yields and a narrow scope of suitable arenes compromised the synthetic advantage of the developed *para*-Csp^2−H amination approach. Herein, we report a further development of the Cu(I)-catalyzed *para*-Csp^2−H amination methodology (eq 5) which addresses the drawbacks mentioned above. Key to the success were the increase in the steric hindrance in iodonium reagent ArI(OH)OTs and the use of strong acid additives as described below. The new conditions feature improved yields and are compatible with a substantially increased scope of arenes.

RESULTS AND DISCUSSION

o-Xylene (**1d**) was selected as a substrate for the method development studies because it was unreactive under the published C−H amination conditions that involved an initial treatment of arene **1d** with MesI(OH)OTs (1.1 equiv) in anhydrous CH_2Cl_2 at room temperature to form an unsymmetrical diaryl-λ^3-iodane **2d**, followed by addition of catalytic amounts of $Cu(MeCN)_4BF_4$, morpholine, DIPEA, and DMSO.[14] We reasoned that the lack of reactivity for **1d** may be attributed to slow formation of an intermediate unsymmetrical diaryl-λ^3-iodane **2d** in the reaction of **1d** with the MesI(OH)OTs reagent. It has been shown that strong acids such as TsOH and TfOH facilitate the formation of diaryl-λ^3-iodanes from arenes.[15] Indeed, addition of TfOH (1.2 equiv) to a mixture of *o*-xylene (**1d**) and MesI(OH)OTs in acetonitrile resulted in the formation of diaryl-λ^3-iodane **2d** in 83% yield. The latter was isolated in pure form and subsequently used for optimization of the Cu(I)-catalyzed reaction with morpholine as shown in Table 1.

The reaction of **2d** with morpholine turned out to be very slow, and the desired product **4d** was formed in only 40% yield after 8 days at room temperature (entry 1). Furthermore, a concomitant formation of the undesired *N*-mesityl morpholine **5d** was also observed (3:1 **4d**:**5d** ratio). A simple change of solvent did not alter the **4d**:**5d** ratio (entry 2). Apparently, insufficient electronic and steric differences between the nontransferable mesityl ligand and xylyl moiety were responsible for the poor regioselectivity of the Cu-catalyzed

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reaction between diaryl-λ^3-iodane **2d** and morpholine. We hypothesized that the increase in the steric demand of the nontransferable aryl ligand in diaryl-λ^3-iodane **2d** could solve the selectivity issue.[16] To this end, unsymmetrical diaryl-λ^3-iodane **3d** possessing a bulky 2,4,6-triisopropylphenyl (TIPP) group was synthesized from *o*-xylene (**1d**) and TIPP-I(OH)-OTs[17] in the presence of TfOH (48% yield of recrystallized material). The structure of **3d** was confirmed by X-ray crystallographic analysis (Figure 1).

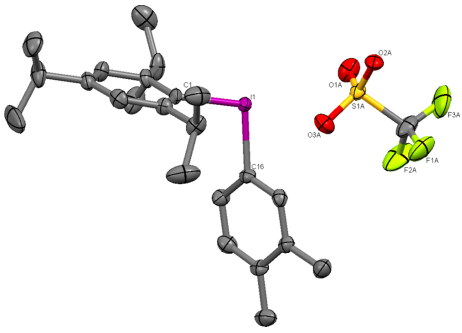

Figure 1. X-ray crystal structure of λ^3-iodane **3d** (ellipsoids at 50% probability) with hydrogen atoms omitted for the sake of clarity. Selected bond distances (angles) and angles (degrees): I1−C1, 2.131(5); I1−C16, 2.118(6); I1−O1A, 3.359(4); I−O3A, 3.513(4); C1−I1−C16, 100.1(2). See the Supporting Information for details.

We were pleased to see that the reaction of diaryl-λ^3-iodane **3d** with morpholine in the presence of the $Cu(MeCN)_4BF_4$ catalyst[18] proceeded with excellent selectivity and formation of the undesired **6** was not observed (Table 1, entry 3). Furthermore, the long reaction time (8 days) could be decreased to merely 12 h with a simple increase in temperature to 40 °C (entry 4). The desired C−H amination product **4d** was isolated in 80% yield. The reaction readily proceeded also in pure DMSO (entry 5). A 2-fold decrease in catalyst loading resulted in a slower reaction that required more time to reach completion (entry 6). Further lowering of the amount of the catalyst (entries 7 and 8) resulted in incomplete conversion of **3d**. Among various Cu(I) sources tested, only CuI was efficient as a catalyst (entry 9). Other Cu(I) salts were less efficient (entries 10 and 11). $Cu(OTf)_2$ could also be used as a catalyst (entry 12); however, the Cu(II)-catalyzed reaction between λ^3-iodane **3d** and morpholine required more time to reach completion compared to the best Cu(I) source (entry 12 vs entry 4). Interestingly, $Cu(BF_4)_2$ hexahydrate was far less efficient as a catalyst than $Cu(MeCN)_4BF_4$ or copper(II) triflate (entry 13 vs entries 4 and 12, respectively). The poor catalytic efficiency of $Cu(BF_4)_2$ hexahydrate could be attributed to the presence of water (0.6 equiv) in the Cu(II) catalyst, because diminished yields of the product **4d** were also observed if C−H amination under the best conditions [with $Cu(MeCN)_4BF_4$ as the catalyst] was performed in the presence of water (10 equiv; entry 14 vs entry 4). On the other hand, the C−H amination reaction mixture always contains water (1 equiv), which forms during λ^3-iodane **3d** formation from starting arene **1d** and TIPP-I(OH)OTs, so the presence of water is likely not responsible for the poor catalytic efficiency of $Cu(BF_4)_2$ hexahydrate. The oxygen-free conditions are important for achieving high yields of C−H amination product **4d** (compare entries 15 and 4). Finally, the reaction of λ^3-iodane **3d** with morpholine in the absence of the Cu(I) catalyst resulted in slow formation of iodoxylene, and the formation of the desired **4d** was not observed (entry 16). It should be noted that the addition of the radical scavenger TEMPO considerably decelerated the formation of iodoxylene, so the noncatalyzed reaction of diaryl-λ^3-iodane **3d** with morpholine presumably proceeds through a radical chain pathway.[14]

The *N*-xylyl-morpholine **4d** could also be synthesized in a sequential one-pot mode without isolation of diaryl-λ^3-iodane **3d**. This required careful control of **3d** formation and the addition of $Cu(MeCN)_4BF_4$, morpholine, $EtN(i\text{-}Pr)_2$, and DMSO to the reaction mixture immediately after the conversion of xylene **1d** to intermediate **3d** was completed. The sequential one-pot two-step C−H amination avoided the isolation and handling of potentially unstable intermediate diaryl-λ^3-iodane **3d** and hence is superior to the stepwise approach.

A series of carbocyclic arenes were subsequently subjected to the one-pot sequential C−H amination to demonstrate the scope of the developed methodology (Table 2). Yields of the two-step sequential C−H amination depended on the ease of formation of unsymmetrical diaryl-λ^3-iodane intermediates as well as on their stability. The formation of iodonium salt intermediates **3a−t** was found to be sensitive to the electronic properties of arene **1**.[19] Toluene (entry 1) represents a reactivity borderline: arenes that are less electron-rich than toluene did not react with TIPP-I(OH)OTs even in the presence of TfOH or TsOH as an additive. *tert*-Butylbenzene was slightly more reactive than toluene (entry 2 vs entry 1), a result that is consistent with the better electron releasing ability of the *tert*-butyl group (σ_p = −0.20) compared to that of the methyl group (σ_p = −0.17).[20] Not surprisingly, arenes possessing two alkyl substituents were readily transformed into diaryl-λ^3-iodane intermediates and, hence, afforded the C−H amination products in 56−62% yields (entries 3−5). It should be noted that all the tested alkyl-substituted arenes (entries 1−5) required TfOH as an additive to afford the unsymmetrical diaryl-λ^3-iodane intermediates. Moderate C−H amination yields for *N*-acetanilide (entry 6) presumably could be attributed to partial acid hydrolysis of the amide moiety.[21] Electron-rich alkoxy-substituted arenes (entries 7−12) readily reacted with TIPP-I(OH)OTs in the presence of TsOH as an additive.[22] Importantly, the strong electron-donating effect of the methoxy group (σ_p = −0.27)[20] compensated for the presence of deactivating electron-withdrawing substituents such as the OCF_3 group (σ_p = +0.35; entry 14) and bromine (σ_p = +0.23; entry 15)[23] and even the sulfonamide moiety (σ_p = +0.65; entry 16). In the latter case, the reaction with TIPP-I(OH)OTs required addition of TfOH and a prolonged time to afford the unsymmetrical diaryl-λ^3-iodane intermediate. It is noteworthy that TIPP-I(OH)OTs-based conditions afforded C−H amination products in yields higher than those determined by the previously published method[14] (see yields in entries 5, 7, 11, and 12). Finally, substituted thiophenes also appeared to be suitable substrates for the developed C−H amination reaction (entries 18−20).

The regioselectivity of the C−H amination is controlled during the formation of the unsymmetrical diaryl-λ^3-iodane intermediates. Notably, all monosubstituted arenes underwent highly regioselective *para*-C−H amination, and the formation

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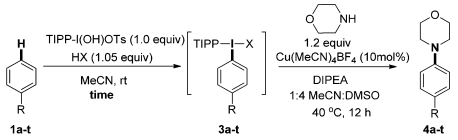
Table 2. Sequential C−H Amination of Arenes 1a−t[a]



TIPP = 2,4,6,-triisopropylphenyl

entry	arene **1**	HX	time (h)	yield **4** (%)[b]	entry	arene **1**	HX	time (h)	yield **4** (%)[b]
1	 **a**	TfOH[c]	3	25	11	 **k**	TsOH	0.2	80(61)[d]
2	 **b**	TfOH[c]	3	35	12	 **l**	TsOH	2	72(49)[d]
3	 **c**	TfOH[c]	2	62	13	 **m**	TsOH	0.2	74
4	 **d**	TfOH[c]	3	62	14[f]	 **n**	TfOH	3	50[g]
5	 **e**	TfOH	3	56(41)[d]	15	 **o**	TfOH	1	70
6	**f**	TfOH	18	49	16	 **p**	TfOH	12	82
7	 **g**	TsOH	2	80(52)[d]	17	 **q**	TfOH[h]	1	44
8	 **h**	TsOH	0.3	66	18	 **r**	TsOH	0.5	49
9	 **i**	TsOH	0.5	71	19	 **s**	TsOH	0.5	44
10	 **j**	none[e]	0.2	55	20	 **t**	TfOH	0.5	62

[a]Conditions: arene **1** (1.2 equiv), acid (1.05 equiv) and TIPP-I(OH)OTs (1.0 equiv) in MeCN (0.5 M) at room temperature, then $Cu(MeCN)_4BF_4$ (10 mol %), morpholine (1.2 equiv), and DIPEA (2.0 equiv) in 1:4 MeCN/DMSO (0.1 M) at 40 °C for 12 h. [b]Average yield of two runs. [c]λ^3-Iodane did not form with TsOH as an additive. [d]In parentheses are yields from ref 14. [e]Performed in CF_3CH_2OH as a solvent without the acid additive. [f]With 1 equiv of $Cu(MeCN)_4BF_4$. [g]Isomeric product **4n′** possessing the morpholine moiety in the *para* position to the OCF_3 group was isolated in 15% yield. [h]At 0 °C with 3 equiv of TfOH and 4 equiv of DIPEA.

of isomeric *ortho*-substituted products generally was not observed.[24] The C−H amination in multiply substituted arenes proceeded selectively at the *para* position to the strongest electron-releasing substituent (entries 11−16). For example, 2,3-dihydrobenzofuran (entry 12) and *N*-tosyl anisidine (entry 13) afforded the C−H amination product in the *para* position to the alkoxy group. In tetrahydroisoquinoline (entry 17), the *para* position with respect to the strongest electron-releasing substituent (MeO group) was blocked, and the reaction took place regioselectively at the sterically less hindered *ortho* position.[25] The regioselective C−H amination of 6-MeO-tetrahydroisoquinoline is noteworthy because this substrate usually affords a mixture of 5- and 7-substituted products in electrophilic halogenation[26] and nitration[27] reactions. 3-Substituted thiophenes underwent C−H amination at position 2 (entries 18−20).

The C−H amination conditions were compatible with the presence of *O*-benzyl (entry 8, Table 2), *O*-allyl (entry 9), and *O*-TBDMS (entry 10) protecting groups as well as the *O*-Me ester moiety (entry 20) and bromide (entry 15). *N*-Trifluoroacetyl (entry 17, Table 2) and *N*-Ts (entry 13) protecting groups were also tolerated. A variety of aliphatic primary amines (entries 1−7, Table 3), aliphatic secondary amines (entries 8−13), aromatic, heteroaromatic amines (entries 14−16), and imidazole (entry 17) could be employed. Azoles possessing relatively acidic N−H bonds such as tetrazole (entry 18) and 1,2,4-triazole (entry 19) also reacted in the presence of DIPEA as the base. Less acidic N−H heterocycles such as indoles did not react under the standard conditions. The reaction of ammonium trifluoroacetate (1.2 equiv) with diaryl-λ^3-iodane **3g** afforded bis(4-methoxyphenyl)amine **26** as the major product (entry 20). Disappointingly, poor conversion (<5%) of diaryl-λ^3-iodane **3g** was observed when aqueous saturated ammonia (10 equiv) or a 2 M solution of NH_3 in methanol (5 equiv) was used as a source of ammonia. Possibly, the formation of a complex with the excess of NH_3 inhibited the Cu(I) catalyst. Nevertheless, the introduction of an NH_2 functional group is possible via the *para*-C−H amination using *N*-allyl (entry 1) or *N*-benzyl amines (entries 3 and 4), followed by N-deprotection of the corresponding anilines **7**, **9**, and **10**, respectively (Table 3).

Importantly, the C−H amination reaction conditions are compatible with the alkene moiety in the amine (entry 1) and *S*-trityl (entry 6) protecting group. Various functional groups such as ethers (entry 4), esters (entry 19), and a bromide (entry 14) are all tolerated. Amines react chemoselectively in the presence of unprotected amide (entry 13) and sulfonamide moieties (entry 15). Monoamination with piperazine is also possible (entry 12).

The developed two-step sequential *para*-C−H amination approach provides a complementary regioselectivity to a Pd-catalyzed method reported by Zhang and co-workers (Scheme 1 and eq 2).[10a] Thus, in their work, the amide-directed C−H amination of arene **1u** with *N*-fluorobenzenesulfonimide (NFSI) proceeded at the *para* position to the amide moiety and afforded *p*-phenylenediamine **27**. In contrast, the regioselectivity of the reaction between arene **1u** and TIPP-I(OH)OTs was controlled by a methoxy group, the strongest

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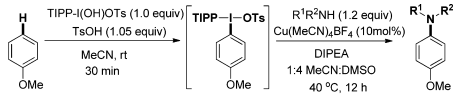
Table 3. Scope of Amines[a]



TIPP = 2,4,6,-triisopropylphenyl

entry	amine	product, yield (%)[b]	entry	amine	product, yield (%)[b]
1		**7**, 77	11		**17**, 56
2		**8**, 70	12[d]		**18**, 50[e]
3		**9**, 73	13		**19**, 61
4		**10**, 77	14		**20**, 74
5		**11**, 44	15		**21**, 49
6[c]		**12**, 42	16		**22**, 20
7		**13**, 72	17[c]		**23**, 76
8		**14**, 63	18[f]		**24**, 79[g]
9		**15**, 78	19[c]		**25**, 39
10		**16**, 80	20		**26**, 33[h]

[a]Conditions: anisole **1g** (1.2 equiv), $TsOH·H_2O$ (1.05 equiv) and TIPP-I(OH)OTs (1.0 equiv) in MeCN (0.5 M) at room temperature for 30 min, then $Cu(MeCN)_4BF_4$ (10 mol %), amine (1.2 equiv), and DIPEA (2.0 equiv) in 1:4 MeCN/DMSO (0.1 M) at 40 °C for 12 h. [b]Average yield of two runs. [c]The reaction of **3g** with amine proceeded within 30 h at 40 °C. [d]DIPEA was not added; piperazine (3.5 equiv) was used both as the nucleophile and as the base. [e]Accompanied by 18% 1,4-bis(4-methoxyphenyl)piperazine. [f]The reaction of **3g** with amine required 40 h at 50 °C and 2.5 equiv of DIPEA. [g]A mixture of 1-aryltetrazole **24a** (35%) and 2-aryltetrazole **24b** (44%). [h]Yield of bis(4-methoxyphenyl)amine **26**; the reaction of **3g** with NH_4OCOCF_3 required 30 h at 40 °C and 3.5 equiv of DIPEA.

electron-releasing substituent in arene **1u**. Subsequent Cu-catalyzed reaction of the unsymmetrical diaryl-λ^3-iodane **3u** intermediate with morpholine produced *p*-anisidine **4u** (Scheme 1). Importantly, a low temperature (−40 °C) was required in the formation step of intermediate **3u** to produce **4u** in good yield (61%).[28]

Finally, a synthesis of antibiotic Linezolid **32** was performed to demonstrate the suitability of the developed Cu-catalyzed *para*-C−H amination method for the late-stage functionalization of lead structures (Scheme 2). The synthesis featured installation of the morpholine moiety in a nonprefunctionalized Linezolid core structure **30** in the final synthetic step. Such an approach streamlines structural variations of the amine moiety and could provide rapid and straightforward access to a number of Linezolid analogues. The synthesis commenced with Cu-catalyzed N-arylation of commercially available oxazolidinone **28**,[29] followed by cleavage of the *N*-Boc protecting group and subsequent N-acetylation to provide the key building block, **30** (Scheme 2). The formation of the unsymmetrical diaryl-λ^3-iodane **31** intermediate took a prolonged time (40 h) to reach completion. Subsequent *in situ* reaction of **31** with morpholine required the presence of stoichiometric amounts[30] of the $Cu(MeCN)_4BF_4$ complex[31] to produce Linezolid **32** in 71% yield (Scheme 2).

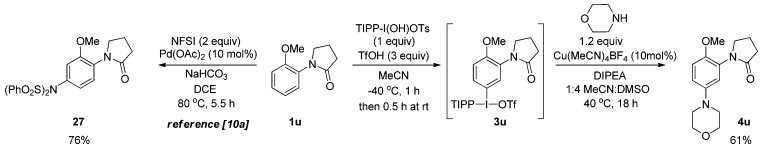
The higher efficiency of the $Cu(MeCN)_4BF_4$ complex compared to that of the representative Cu(II) complex (entry 12 vs entry 4, Table 1) suggests that Cu(I) salts are the catalytically active species and Cu(II) salts are *in situ* reduced to the active Cu(I) catalyst by amine.[32] Such a scenario is consistent with our earlier observation that selective trapping of Cu(I) species with neocuproine [a highly specific chelating agent for Cu(I) ions] resulted in the complete inhibition of the C−H amination reaction.[14] Consequently, a Cu^I/Cu^{III} catalytic cycle for the reaction between unsymmetrical λ^3-iodanes **3** and amines is plausible.[33] It would start with an initial formation of Cu(I)−diamine complex **I**, followed by oxidative addition of λ^3-iodane **3** to form Cu(III) intermediate **II** and be completed by product-forming reductive elimination to afford a C−H amination product and to regenerate a catalytically active Cu(I) species (Scheme 3).

Unfortunately, the proposed transient Cu(III) complexes could not be detected, presumably because they undergo rapid C−N bond forming reductive elimination.[34] This behavior is expected because related, highly reactive Cu(III) species have been observed only in chelation-stabilized complexes based on stabilizing triazamacrocyclic ligands.[35] Further mechanistic studies are necessary to fully elucidate the mechanism of the developed C−H amination approach.

■ CONCLUSIONS

In summary, the use of bulky 2,4,6-triisopropylphenyl (TIPP) group-containing iodonium reagent TIPP-I(OH)OTs together with strong acid additives such as TsOH and TfOH allowed for a substantial increase in substrate scope and improvement of C−H amination yields compared to those of the previously published method.[14] The new conditions are suitable for *para*-selective C−H amination of a wide range of relatively electron-rich arenes. The high *para* regioselectivity of the C−H amination is controlled at the stage of the formation of the unsymmetrical diaryl-λ^3-iodane intermediates. Although the regioselectivity is a result of the combined directing effects of arene substituents, in general it is consistent with that of electrophilic aromatic substitution (S_EAr) reactions. Thus, the C−H amination takes place at the *para* position to the strongest electron-releasing substituent. Hammett substituent σ constants can be used to predict the regioselectivity of the C−H amination in carbocyclic arenes possessing multiple substituents. The developed method provides a complementary

Scheme 1. Complementary Regioselectivity of Different C−H Amination Methods



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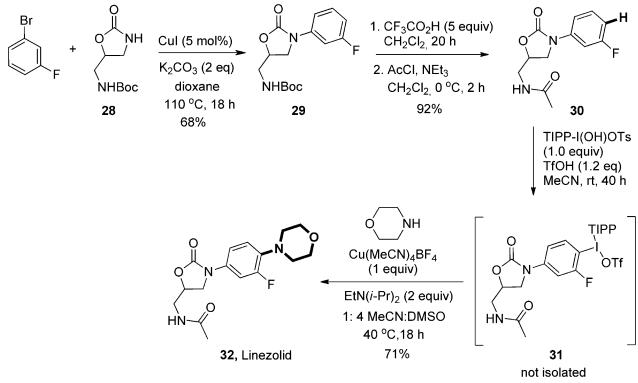
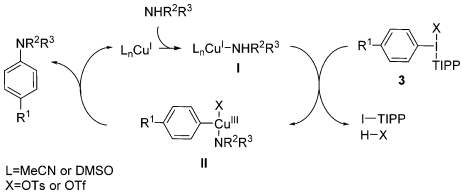
Scheme 2. Synthesis of Linezolide 32 by Late-Stage C−H Amination



Scheme 3. Working Mechanism for C−H Amination of Arenes



regioselectivity to the well-developed *ortho*-C−H amination approach, and it may be especially useful for late-stage *para*-regioselective C−H amination of pharmaceutically relevant carbocyclic arenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01992.

Experimental details, characterization data, and NMR spectra of λ^3-iodane **3d** (PDF)

X-ray crystallographic data of λ^3-iodane **3d** (CIF)

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Notes

The authors declare no competing financial interest.

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(21) An equimolar amount of water was formed in the reaction of TIPP-I(OH)OTf with arene.

(22) Addition of TfOH to electron-rich arenes resulted in an exotherm and formation of more side products.

(23) Trifluoromethoxybenzene and bromobenzene do not react with ArI(OH)OTs in the presence of TfOH.

(24) The formation of regioisomeric *ortho*-C−H amination side product **4n′** was observed only for 3-(trifluoromethoxy)anisole **4n** (50:14 *para*:*ortho*).

(25) The major side product was the corresponding 3,4-dihydroisoquinoline, which presumably was formed by acidic hydrolysis of **1q** followed by oxidation of the intermediate 1,2,3,4-tetrahydroisoquinoline by I(III) species. *N*-Acetyl tetrahydroisoquinoline (related to **1q**) was less stable toward the acidic hydrolysis.

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(28) At room temperature, intermediate diaryliodonium triflate **3u** appeared to be unstable. Among major decomposition products there was the O-Tf analogue of **4u**, which apparently was formed by C−O bond forming reductive elimination from **3u**. For thermally unstable intermediate iodanes, the use of low temperatures is recommended.

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(31) Copper(I) iodide in stoichiometric amounts is incompatible with the C−H amination conditions because it acts as a source of iodide and affords the C−H iodination product instead of the desired Linezolid **32**. However, CuI can be employed in catalytic amounts (10 mol%; see entry 9 of Table 1).

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V

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of Electron-rich Arenes and Heteroarenes"
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Para-Selective Cu-Catalyzed C−H Aryloxylation of Electron-Rich Arenes and Heteroarenes

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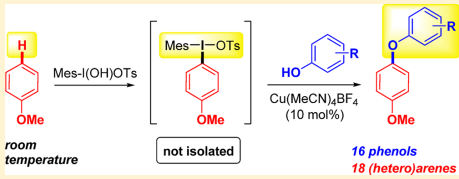
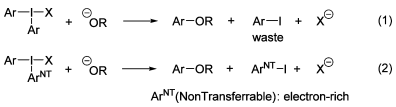
Supporting Information

ABSTRACT: Cu-catalyzed reaction of phenols with electron-rich arene or heteroarene ligands of unsymmetrical diaryl-λ^3-iodanes is a key step in the developed one-pot two-step method for intermolecular *para*-selective C−H aryloxylation of heteroarenes and arenes.



INTRODUCTION

Synthetic methodologies employing hypervalent iodonium species have recently become an important alternative to the transition-metal-catalyzed direct Csp^2−H activation methods for C−O bonds formation.[1,2] Thus, a reaction of diaryliodonium salts with various oxygen nucleophiles such as alcohols and phenols under metal-free conditions has been widely used for synthesis of aryl alkyl ethers and diaryl ethers.[3,4] The use of symmetrical diaryliodonium salts in the reaction with oxygen nucleophiles generates 1 equiv of aryl iodide side product together with the desired ether (eq 1).The aryl iodide



nucleofuge waste becomes cost-inefficient for diaryliodonium salts possessing structurally complex aryl moieties. Therefore, unsymmetrical diaryliodonium salts comprising an elaborated aryl moiety and structurally simple nontransferrable or "dummy" arene ligand are often used (eq 2). The nontransferrable aryl moieties should be relatively electron-rich and sterically unhindered because oxygen nucleophiles such as phenolates react either with the most electron-deficient of the two aryl moieties in the unsymmetrical iodonium salt (electronic control) or with an *ortho*-substituted aryl moiety (steric control or so-called *ortho* effect).[5,6] Such a reactivity pattern, however, imparts an important limitation to the transition-metal-free methodology: oxygen nucleophiles apparently do not react with electron-rich aryl moieties of unsymmetrical diaryliodonium species.

We have recently demonstrated that the selectivity of the reaction between unsymmetrical diaryl-λ^3-iodanes and nitrogen nucleophiles such as azides and amines can be directed to the more electron-rich arene or heteroarene moiety by a Cu(I) catalyst.[7,8] We report herein that the most electron-rich of the two aryl ligands in unsymmetrical diaryliodonium species react selectively with oxygen nucleophiles such as phenols in the presence of Cu(I) species.[9] This finding provided new opportunities for Csp^2−H functionalization of arenes given that the unsymmetrical diaryl-λ^3-iodanes can be generated in situ directly from relatively electron-rich arenes and hypervalent iodonium reagent such as ArI(OH)OTs.[10] We envisioned that the electron-rich aryl moiety of the in situ formed unsymmetrical diaryl-λ^3-iodanes would subsequently react with phenols in the presence of Cu(I) catalyst to afford diaryl ethers. Indeed, we found that the transformation of non-prefunctionalized arenes to diaryl ethers can be performed in a sequential two-step manner as described below. Furthermore, the developed Csp^2−H aryloxylation approach features high *para*-selectivity of C−O bond formation, and hence, it is a complementary methodology to transition-metal-catalyzed Csp^2−H to Csp^2−O transformations which usually requires the presence of an *ortho*-directing group in the arene.[11]

RESULTS AND DISCUSSION

p-Methoxyphenyl-containing diaryl-λ^3-iodane **2e**[12] was chosen as a model for the development of a Csp^2−H aryloxylation method because the *p*-anisyl moiety has been frequently used as a "dummy" ligand in the noncatalyzed reactions of unsymmetrical diaryl-λ^3-iodanes with oxygen nucleophiles.[13] Indeed, phenol **3a** reacted preferentially with a mesityl ligand of the λ^3-iodane **2e** to afford mesityl 4-bromophenyl ether and iodoanisole **5** (entry 1, Table 1). The desired **4e** was formed in less than 5% yield. In sharp contrast, addition of $Cu(MeCN)_4BF_4$ (10 mol %) altered the selectivity of the reaction, providing ether **4e** as the major product (**4e**:**5** = 2:1, entry 2). The mesityl moiety apparently served as a nontransferable aryl ligand[14] in the Cu(I)-catalyzed reaction

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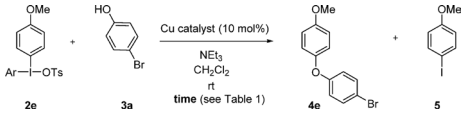
Table 1. Reaction of λ^3-Iodane 2e with Phenol 3a[a]



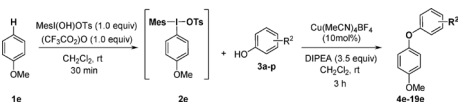
entry	λ^3-iodane	Cu catalyst	time[b] (h)	4e[c] (%)	5[c] (%)
1	**2e**	none	168[d]	<5	55[e]
2	**2e**[f]	$Cu(MeCN)_4BF_4$	1.5	60	33
3	**2e-Ph**[g]	$Cu(MeCN)_4BF_4$	1.5	49	47
4	**2e-TIPP**[h]	$Cu(MeCN)_4BF_4$	1.5	30	66
5	**2e**	CuI	1.5	49	36
6	**2e**	$Cu(OTf)_2$	48	30	51
7	**2e**	CuOTf	48	33	50
8[i]	**2e**	$Cu(MeCN)_4BF_4$	48	30	47
9[j]	**2e**	$Cu(MeCN)_4BF_4$	1.5	49	38

[a]Conditions: λ^3-iodane **2e** (1 equiv), phenol **3a** (1.2 equiv), *i*-$PrNEt_2$ (1.5 equiv), CH_2Cl_2 (0.1 M). [b]Full conversion of **2e**. [c]Determined by ^1H NMR using methyl 2-iodobenzoate as an internal standard. [d]75% conversion of **2e**. [e]Formed together with 20% of mesityl 4-bromophenyl ether. [f]Ar = Mes. [g]Ar = Ph. [h]Ar = TIPP (2,4,6-triisopropyl)phenyl. [i]In the presence of water (1 equiv). [j]Under air.

of λ^3-iodane **2e** with **3a**. As anticipated, replacement of bulky mesityl ligand for a less sterically hindered phenyl group (iodane **2e-Ph**) resulted in a nonselective reaction (entry 3). Disappointingly, the use of sterically highly hindered triisopropylphenyl (TIPP) ligand as the nontransferable aryl moiety[15] (iodane**2e-TIPP**) resulted in undesired selectivity (**4e**:**5** = 1:3, entry 4). Therefore, the mesityl group was chosen as the "dummy" ligand in all subsequent experiments. Copper(I) iodide can be used as a catalyst at the expense of slightly diminished yields of the target **4e** (**4e**:**5** = 1.4:1, entry 5). Interestingly, catalytic efficiency of copper salts depended on the structure of anion: both Cu(I) and Cu(II) triflates were inferior to $Cu(MeCN)_4BF_4$ (entries 6 and 7 vs entry 2). The presence of water (1 equiv) was found to be detrimental for the success of the reaction between λ^3-iodane **2e** and **3a** (entry 8). Hence, moisture-free conditions are critical to obtain the desired product **4e** in good yields. The presence of oxygen had a relatively small effect on the reaction outcome (entry 9 vs entry 2).

With the optimized conditions for the reaction between λ^3-iodane **2e** and phenol **3a** in hand, the development of a one-pot sequential synthesis of diaryl ethers from non-prefunctionalized arenes without isolation of the intermediate λ^3-iodane was addressed. The λ^3-iodane **2e** could be formed from anisole and MesI(OH)OTs (1.1 equiv) in 74% yield within 24 h in anhydrous CH_2Cl_2 at room temperature. Higher yields of **2e** were achieved in the presence of protic acids such as CF_3COOH and TsOH (82% and 91%, respectively).[16] Subsequent reaction of the in situ formed **2e** with phenol **3a** in the presence of *i*-$PrNEt_2$ (2.5 equiv) and $Cu(MeCN)_4BF_4$ (10 mol %) afforded the desired diaryl ether **4e** in 57% yield after 18 h at room temperature. The prolonged reaction time could be decreased substantially by capturing 1 equiv of water that is generated during the formation of λ^3-iodane **2e** from anisole and MesI(OH)OTs (compare entries 8 and 2, Table 1). This was achieved by using trifluoroacetic acid anhydride (1 equiv) as an additive. The anhydride reacted with water to form trifluoroacetic acid which, in turn, facilitated the formation of λ^3-iodane **2e** in 70% yield within 3 h at room temperature (entry 1, Table 2).

Table 2. Scope of Phenols 3[a]



entry	ArOH **3**	yield, %[b]	entry	ArOH **3**	yield, %[b]
1	**a**	**4e**, 70	9	**i**	**12e**, 37
2	**b**	**5e**, 65	10	**j**	**13e**, 64
3	**c**	**6e**, 73	11	**k**	**14e**, 50
4	**d**	**7e**, 68	12	**l**	**15e**, 67
5	**e**	**8e**, 69	13	**m**	**16e**, 54
6	**f**	**9e**, 59	14	**n**	**17e**, 75
7	**g**	**10e**, 50	15	**o**	**18e**, 67
8	**h**	**11e**, 58	16	**p**	**19e**, 53

[a]Conditions: arene **1e** (1.0 equiv), $(CF_3CO)_2O$ (1.0 equiv) and MesI(OH)OTs (1.0 equiv) in CH_2Cl_2 (0.25 M) at room temperature for 30 min, then $Cu(MeCN)_4BF_4$ (10 mol %), phenol **3** (1.2 equiv) and DIPEA (3.5 equiv) in CH_2Cl_2 (0.1 M) at rt for 3 h. [b]Average yield of two runs.

Next, the scope of phenols suitable for the reaction with λ^3-iodane **2e** was examined (Table 2). Phenols with both electron-withdrawing groups (entries 2, 4, 9, 11, and 14) and electron-releasing groups (entries 6, 8, and 12) are suitable as nucleophiles. Sterically hindered phenols (entries 8 and 9) afforded lower yields of diaryl ethers. The C−H aryloxylation conditions are compatible with a variety of functional groups in phenols such as halides (entry 1, 9, and 16), nitro group (entry 2), carboxylic ester (entries 4 and 5), amide (entry 11), benzylic alcohol (entry 13), aldehyde (entry 14), alkene (entry 10), and *N*-Boc protecting group (entry 12). Quinolin-6-ol (entry 7) and hydroxypyridines (entries 15 and 16) could be also used as nucleophiles.

All arenes that react with MesI(OH)OTs reagent in the presence of trifluoroacetic anhydride and form relatively stable λ^3-iodanes are suitable as substrates (Table 3). Toluene **1a** (entry 1) represents a reactivity borderline: less electron-rich arenes than toluene (for example, benzene and aryl halides) did not react with MesI(OH)OTs reagent. Time of the formation of λ^3-iodanes **2a**−**r** correlated well with electronic properties of the starting arenes **1a**−**r**: the more electron-rich were arenes **1a**−**r**, and the shorter time was required to achieve complete conversion to λ^3-iodanes **2a**−**r** (compare entries 1, 3, 5, and 12 as well as entries 4 and 10, Table 3). The strong electron-donating effect of methoxy group (σ_p = −0.27)[17] compensated for the presence of deactivating electron-withdrawing substituents such as bromine (entry 9) and amide (entry 13). Relatively electron-rich heterocycles such as thiophene (entry

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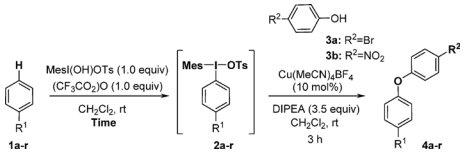
Table 3. Substrate Scope for the Synthesis of Diaryl Ethers[a]



entry	arene **1**	ArOH	time, h	yield, %[b]	entry	arene **1**	ArOH	time, h	yield, %[b]
1	**a**	**3a**	40	63	10	**j**	**3a**	0.1	57
2	**b**	**3a**	18	67	11	**k**	**3a**	2	65[c]
3	**c**	**3a**	3	72	12	**l**	**3a**	0.25	55
4	**d**	**3a**	0.5	51	13	**m**	**3a**	0.5	28
5	**e**	**3a**	0.5	70	14	**n**	**3b**	0.5	50
6	**f**	**3a**	0.5	73	15	**o**	**3b**	0.5	71
7	**g**	**3a**	0.5	78	16	**p**	**3b**	18	53
8	**h**	**3a**	0.5	68	17	**q**	**3b**	0.25	49
9	**i**	**3a**	18	65	18	**r**	**3b**	0.5	43

[a]Conditions: arene or heteroarene **1** (1.0 equiv), $(CF_3CO)_2O$ (1.0 equiv), and Mes-I(OH)OTs (1.0 equiv) in CH_2Cl_2 (0.25 M) at room temperature, then $Cu(MeCN)_4BF_4$ (10 mol %), phenol **3** (1.2 equiv) and DIPEA (3.5 equiv) in CH_2Cl_2 (0.1 M) at rt for 3 h. [b]Average yield of two runs. [c]80% purity according to ^1H NMR; pure product (>95%) was obtained by crystallization.

14), indoles (entries 15 and 16), and pyrroles (entries 17 and 18) also afforded the C−H aryloxylation products.

Regioselectivity of the C−H aryloxylation is controlled at the stage of the formation of the unsymmetrical diaryl-λ^3-iodane intermediates **2a−r**. Notably, all monosubstituted arenes underwent highly regioselective *p*-C−H aryloxylation, and the formation of isomeric *ortho*-substituted products was not observed. The C−O bond formation in multiply substituted arenes proceeded selectively at the *para*-position to the strongest electron-releasing substituent (entries 9−11). In heterocycles, the regioselectivity of the C−O bond formation was consistent with that of electrophilic aromatic substitution (S_EAr) reactions: λ^3-iodanes were formed at the β-position of indoles (entries 15 and 16, Table 3) and at the α-position of thiophenes (entry 14) and pyrroles (entry 17). In 2,5-disubstituted pyrrole, the C−H aryloxylation occurred at the β-position (entry 18).

The C−H aryloxylation conditions were compatible with the presence of bromine (entries 9, 15, 16, and 18) and even pinacolyl boronate moiety (entry 11) in substrates, which renders feasible their further functionalization. *O*-Allyl (entry 6), *O*-benzyl (entry 7), *N*-benzyl (entry 18), and even relatively labile *O*-TBDMS (entry 8) protecting groups are tolerated. Heteroarenes may contain a range of functional groups such as secondary amides (entry 13), carboxylic esters (entries 15, 17, and 18), and nitrile (entry 16).

An important mechanistic question pertains to possible involvement of phenoxy diaryl-λ^3-iodanes in the Cu-catalyzed aryloxylation reaction. Putative phenoxy diaryl-λ^3-iodanes could form from tosyloxy diaryl-λ^3-iodanes **2a−r** and phenols by exchange of tosyloxy ligand for phenoxy moiety. Subsequent Cu-catalyzed reductive elimination from phenoxy diaryl-λ^3-iodanes would afford diaryl ethers and iodomesitylene. To verify such a mechanistic scenario, preparation of phenoxy diaryl-λ^3-iodanes in pure form was attempted. After considerable work, it was found that relatively stable phenoxy diaryl-λ^3-iodanes could be obtained from the corresponding tosylates only if phenols possessing electron-withdrawing substituents were used. Thus, the reaction of sodium *p*-nitrophenolate and iodonium tosylate **2o** afforded crystalline phenoxy diaryl-λ^3-iodane **20**, which could be stored for more than a week at 4 °C without decomposition. The structure of **20** was confirmed by X-ray crystallographic analysis (Figure 1).[18]

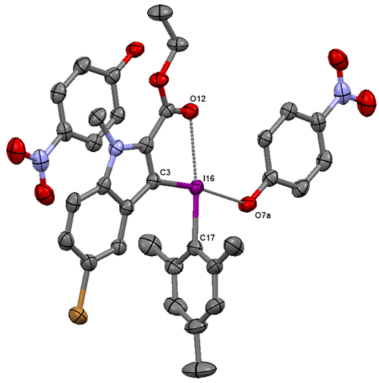


Figure 1. X-ray crystal structure of a 1:1 adduct of λ^3-iodane **20** and phenol **3b** (thermal displacement ellipsoids are drawn at the 50% probability level and hydrogen atoms are omitted for clarity). Selected bond distances (Å) and angles (deg): I16−C3, 2.095(3); I16−C17, 2.102(3); I16−O7a, 2.578(2); I−O12, 2.748(2); C3−I16−C17, 95.0(1). See the Supporting Information for details.

In CH_2Cl_2 solution, phenoxy diaryl-λ^3-iodane **20** undergoes slow reductive elimination to form 3-iodoindole **21** and diaryl ether **22** (eq 3; 25% conversion after 3 h at rt; 100% conversion after 168 h at rt), and the formation of **4o** was not observed. Importantly, addition of $Cu(MeCN)_4BF_4$ (10 mol %) resulted in reversal of selectivity favoring the formation of the desired ether **4o** (**4o**:**21** = 5:1) together with Mes-I (eq 4). Furthermore, the copper catalyst considerably decreased the reaction time (complete conversion of **20** was observed already after 1.5 h). These results point toward an involvement of phenoxy diaryl-λ^3-iodane intermediates such as **20** in catalytic cycle of the Cu-catalyzed C−H aryloxylation.

A control experiment has been carried out to determine the oxidation state of catalytically active copper species in the C−H aryloxylation reaction. Accordingly, neocuproine (2 equiv with respect to $Cu(MeCN)_4BF_4$) was added to the λ^3-iodane **20** and Cu(I) catalyst (eq 5). Neocuproine is a highly specific chelating agent for Cu(I) ions, which forms a stable bright orange-colored complex of formula Cu^I(neocuproine)$_2$.[19] The addition of neocuproine considerably decelerated the reaction and only 15% conversion of λ^3-iodane **20** was observed after 6 h as

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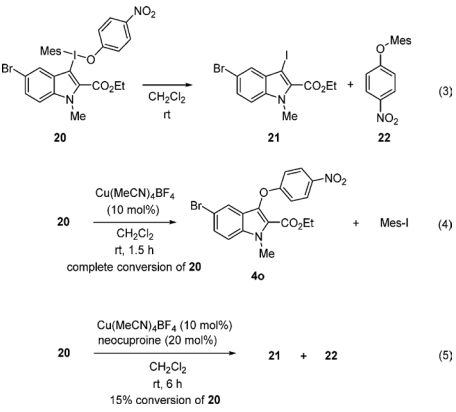

opposed to the complete conversion of **20** within 1.5 h without the added neocuproine (eq 5 vs eq 4).[20] Furthermore, 3-iodoindole **21** and ether **22** were the only products observed in the reaction mixture and the desired **4o** was not formed. Evidently, the addition of neocuproine completely inhibited the Cu(I)-catalyzed reaction and λ^3-iodane **20** underwent slow noncatalyzed conversion to **21** and **22**. On the basis of these results, a Cu^{I}/Cu^{III} catalytic cycle for the reaction between λ^3-iodanes **2** and phenols **3** is plausible. Accordingly, an initially formed Cu(I) phenolate would undergo oxidative addition of the λ^3-iodane **2** to form the Cu(III) intermediate. Product-forming reductive elimination would afford diaryl ether and regenerate a catalytically active Cu(I) species.

CONCLUSIONS

In summary, electron-rich arene or heteroarene ligands of unsymmetrical diaryl-λ^3-iodanes undergo reaction with phenolates in the presence of Cu(I) catalyst. Such a reactivity mode of unsymmetrical diaryl-λ^3-iodanes with phenolates cannot be achieved under metal-free conditions where electronically poor arene ligands react preferentially. Hence, the Cu(I)-catalyzed synthesis of diaryl ethers from unsymmetrical diaryl-λ^3-iodanes is a complementary method to the metal-free conditions. The Cu(I)-catalyzed reaction between unsymmetrical diaryl-λ^3-iodanes and phenolates was used also as a key step in the development of a one-pot, two-step sequential catalytic C−H aryloxylation method. The C−H aryloxylation method comprised an initial formation of unsymmetrical diaryl-λ^3-iodanes directly from non-prefunctionalized electron-rich arenes or heteroarenes and MesI(OH)OTs reagent. Subsequent Cu(I)-catalyzed reaction of the in situ formed unsymmetrical diaryl-λ^3-iodanes with phenolates provided the desired diaryl ethers. The developed C−H aryloxylation method features high *para*-selectivity of C−H aryloxylation of a wide range of relatively electron-rich arenes. The *para* regioselectivity is controlled at the stage of the formation of the unsymmetrical diaryl-λ^3-iodane intermediates. Regioselectivity of C−H aryloxylation in heteroarenes in general is consistent with that of electrophilic aromatic substitution (S_EAr) reactions. Given the mild reaction conditions (room temperature) and excellent functional group compatibility, the developed C−H aryloxylation is especially suitable for late-stage *para*-selective functionalization of pharmaceutically relevant arenes and heteroarenes.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all chemicals were used as obtained from commercial sources, and all reactions were performed under argon atmosphere. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel F-254 plates. Nuclear magnetic resonance spectra were recorded on NMR spectrometers at the following frequencies: ^{1}H, 400 or 300 MHz; $^{13}C\{^1H\}$, 101 or 75 MHz. Chemical shifts are reported in parts per million (ppm) relative to TMS or with the residual solvent peak as an internal reference. Infrared (IR) spectra were recorded with KBr pellet, and wavenumbers are given in cm^{-1}. High-resolution mass spectra (HRMS) were recorded on a TOF MS instrument using the ESI technique.

Preparation of Unsymmetrical Diaryl-λ^3-iodanes. *(4-Methoxyphenyl)[[(4-methylphenyl)sulfonyl]oxy](2,4,6-trimethylphenyl)-λ^3-iodane (**2e**).* To a well-stirred suspension of MesI(OH)OTs (2.17 g, 5.00 mmol, 1.0 equiv) and TsOH·H_2O (951 mg, 5.00 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) was added dropwise neat anisole **1e** (543 μL, 5.00 mmol, 1.00 equiv), and the resulting yellow solution was stirred at room temperature. The progress of the reaction was monitored by TLC (disappearance of the MesI(OH)OTs spot, R_f = 0.49, 20:80:5 MeOH/CH_2Cl_2/AcOH) and complete conversion of the starting material was observed within 1 h. The solution was concentrated to ca. 2/3 of the original volume, and Et_2O was added (50 mL). The formed precipitate was filtered, washed with Et_2O (10 mL), and dried in vacuo to afford **2e** as a white powder (2.50 g, 95% yield). Pure material was obtained by crystallization from CH_2Cl_2/diethyl ether: mp 180 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 7.95−7.89 (2H, m), 7.49−7.44 (2H, m), 7.19 (2H, s), 7.12−7.08 (2H, m), 7.06−7.00 (2H, m), 3.78 (3H, s), 2.60 (6H, s), 2.28 (6H, s). The ^{1}H NMR spectrum was in agreement with that reported in the literature.[21]

*(4-Methoxyphenyl)[[(4-methylphenyl)sulfonyl]oxy][2,4,6-tris(1-methylethyl)phenyl]-λ^3-iodane (**2e-TIPP**).* Iodane **2e-TIPP** (2.33 g, 77% yield) was synthesized from TIPP-I(OH)OTs[22] (2.59 g, 5.00 mmol, 1.0 equiv), TsOH·H_2O (951 mg, 5.00 mmol, 1.0 equiv), and anisole **1e** (543 μL, 5.00 mmol, 1.00 equiv) as described for iodane **2e**. Pure material was obtained by crystallization from CH_2Cl_2/diethyl ether: mp 168 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 7.91−7.84 (2H, m), 7.49−7.44 (2H, m), 7.28 (2H, s), 7.14−7.05 (4H, m), 3.78 (3H, s), 3.49−3.38 (2H, m), 3.03−2.89 (1H, m), 2.28 (3H, s), 1.26−1.17 (18H, m). The ^{1}H NMR spectrum was in agreement with that reported in the literature.[13d]

*(4-Methoxyphenyl)[[(4-methylphenyl)sulfonyl]oxy]phenyl-λ^3-iodane (**2e-Ph**).* Iodane **2e-Ph** (2.3 g, 95% yield) was synthesized from $PhI(OAc)_2$ (1.61 g, 5.00 mmol, 1.0 equiv), TsOH·H_2O (1.24 g, 6.5 mmol, 1.3 equiv), and anisole **1e** (543 μL, 5.0 mmol, 1.00 equiv) as described for iodane **2e**. Pure material was obtained by crystallization from CH_2Cl_2/diethyl ether: mp 160 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 8.23−8.13 (4H, m), 7.68−7.61 (1H, m), 7.55−7.44 (4H, m), 7.14−7.04 (4H, m), 3.79 (3H, s), 2.28 (3H, s).The ^{1}H NMR spectrum was in agreement with that reported in the literature.[10a]

*Ethyl 5-Bromo-1-methyl-3-[(4-nitrophenoxy)(2,4,6-trimethylphenyl)-λ^3-iodanyl]-1H-indole-2-carboxylate 1:1 Adduct with 4-Nitrophenol (**20**).* A solution of ethyl 5-bromo-3-(mesityl(tosyloxy)-λ^3-iodanyl)-1-methyl-1*H*-indole-2-carboxylate[8a] (2.0 g, 2.86 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was extracted twice with a solution of 4-nitrophenol (598 mg, 4.30 mmol, 1.5 equiv) and NaOH (172 mg, 4.30 mmol, 1.5 equiv) in water (50 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo, and Et_2O (50 mL) was added to the yellow residue. Formed precipitate was filtered, washed with Et_2O (10 mL), and dried in vacuo to afford λ^3-iodane **20** as a yellow powder (1.53 g, 67% yield). Pure material was obtained by crystallization from CH_2Cl_2/diethyl ether: mp 124 °C dec; IR (film, cm^{-1}) 1717 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 11.25−10.50 (1H, br s), 7.99−7.94 (4H, m), 7.41 (1H, dd, *J* = 9.0, 1.8 Hz), 7.30 (1H, d, *J* = 9.0 Hz), 7.05 (2H, s), 6.61−6.57 (4H, m), 5.96 (1H, d, *J* = 1.8 Hz), 4.58 (2H,

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q, J = 7.1 Hz), 4.08 (3H, s), 2.56 (6H, s), 2.35 (3H, s), 1.50 (3H, t, J = 7.1 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 169.71, 169.68, 161.8, 144.9, 143.1, 138.9, 137.9, 129.99, 129.97, 129.0, 127.2, 126.6, 122.3, 119.8, 117.4, 116.5, 113.2, 64.0, 33.6, 27.3, 21.2, 14.5; HRMS-ESI (m/z) calcd for $C_{21}H_{22}NO_2BrI$ $[M - OC_6H_4NO_2{*}HOC_6H_4NO_2]^+$ 525.9879, found 525.9878.

Preparation of $Cu(MeCN)_4BF_4$. $[Cu(MeCN)_4]BF_4$ was synthesized in accordance with the literature procedure.[23] Thus, to a blue-colored suspension of $Cu(BF_4)_2{\cdot}6H_2O$ (2.00 g, 5.79 mmol) in anhydrous MeCN (50 mL) was added copper powder (1.47 g, 23.17 mmol). The resulting suspension was heated under reflux for 4 h under argon atmosphere and then hot-filtered. The pale blue filtrate was then cooled to −20 °C whereupon a white solid crystalline material was formed. The white solid was collected by filtration and washed with Et_2O (15 mL). Pure material was obtained by recrystallization from hot MeCN. Yield: 1.73 g (95%).

General Procedure for Sequential One-Pot, Two-Step Synthesis of Diarylethers. To a solution of MesI(OTs)OH (217 mg, 0.50 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (1 mL) under argon atmosphere was added a solution of arene **1** (0.50 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (1 mL). Neat TFAA (71 μL, 0.50 mmol, 1.0 equiv) was then added dropwise (*slowly, within 2−3 min; too fast addition of TFAA leads to the formation of side products*). The resulting solution (color range−pale yellow to dark brown) was stirred at room temperature under argon atmosphere, and the progress of the reaction was monitored by TLC (disappearance of the starting I (III) reagent spot; mobile phase 20:80:5 MeOH/DCM/AcOH). Immediately upon disappearance of MesI(OTs)OH reagent (see Table 3 for appropriate time), the reaction mixture was transferred via cannula to another flask which contained preweighed solid $[Cu(MeCN)_4]^+BF_4^-$ (16 mg, 0.05 mmol, 10 mol %) and a magnetic stir bar, and the source flask was rinsed with CH_2Cl_2 (1 mL). To the resulting well-stirred suspension was immediately (!) added a solution of phenol (0.6 mmol, 1.2 equiv) in anhydrous CH_2Cl_2 (2 mL), followed by neat DIPEA (305 μL 1.75 mmol, 3.5 equiv) (*Important! Decomposition of the formed λ^3-iodane begins if the addition of Cu catalyst and/or DIPEA is delayed.*) The resulting solution was stirred at room temperature under argon atmosphere, and the progress of the reaction was monitored by TLC (mobile phase MeOH/CH_2Cl_2/AcOH = 20:80:5; the intermediate λ^3-iodanes have R_f = 0.4−0.6). In most cases, the reaction was completed in 3 h. The solution was poured into a mixture of water (50 mL) and aqueous saturated ammonia solution (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel.

*1-Bromo-4-(4-methoxyphenoxy)benzene (**4e**).*[24] Following the general procedure, anisole **1e** (54 μL, 0.50 mmol) was converted into **4e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% light petroleum ether to 15% EtOAc in light petroleum ether afforded product as a pale yellow powder (100 mg in the first run and 95 mg in the second run, 72% and 68% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f = 0.35. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 87−88 °C; ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 7.42−7.35 (2H, m), 7.00−6.94 (2H, m), 6.92−6.86 (2H, m), 6.85−6.78 (2H, m), 3.81 (3H, s).

*1-Methoxy-4-(4-nitrophenoxy)benzene (**5e**).*[25] Following the general procedure, anisole **1e** (54 μL, 0.50 mmol) was converted into **5e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% light petroleum ether to 15% EtOAc in light petroleum ether afforded product as a white powder (75 mg in the first run and 85 mg in the second run, 61% and 69% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f = 0.29. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 113−114 °C; ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 8.21−8.15 (2H, m), 7.06−7.00 (2H, m), 6.99−6.92 (4H, m), 3.84 (3H, s).

*1-Methoxy-4-phenoxybenzene (**6e**).*[25] Following the general procedure, anisole **1e** (54 μL, 0.50 mmol) was converted into **6e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% light petroleum ether to 15% EtOAc in light petroleum ether afforded product as a colorless oil (75 mg in the first run and 70 mg in the second run, 75% and 70% yield, respectively): analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f = 0.46; ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 7.33−7.27 (2H, m), 7.07−7.01 (1H, m), 7.01−6.96 (2H, m), 6.96−6.91 (2H, m), 6.91−6.85 (2H, m), 3.81 (3H, s).

*Ethyl 4-(4-Methoxyphenoxy)benzoate (**7e**).*[26] Following the general procedure, anisole **1e** (54 μL, 0.50 mmol) was converted into **7e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% light petroleum ether to 15% EtOAc in light petroleum ether afforded product as a colorless oil (95 mg in the first run and 90 mg in the second run, 70% and 66% yield, respectively): analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f = 0.29; ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 8.02−7.95 (2H, m), 7.05−6.98 (2H, m), 6.96−6.89 (4H, m), 4.35 (2H, q, J = 7.1 Hz), 3.82 (3H, s), 1.38 (3H, t, J = 7.1 Hz).

*Methyl [4-(4-Methoxyphenoxy)phenyl]acetate (**8e**).*[27] Following the general procedure, anisole **1e** (54 μL, 0.50 mmol) was converted into **8e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% light petroleum ether to 15% EtOAc in light petroleum ether afforded product as a colorless oil (91 mg in the first run and 95 mg in the second run, 67% and 70% yield, respectively): analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f = 0.21; ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 7.24−7.17 (2H, m), 7.01−6.94 (2H, m), 6.93−6.84 (4H, m), 3.81 (3H, s), 3.70 (3H, s), 3.59 (2H, s).

*5-(4-Methoxyphenoxy)-1,3-benzodioxole (**9e**).*[28] Following the general procedure, anisole **1e** (54 μL, 0.50 mmol) was converted into **9e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% light petroleum ether to 15% EtOAc in light petroleum ether afforded product as a colorless oil (70 mg in the first run and 75 mg in the second run, 57% and 61% yield, respectively): analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f = 0.33; ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 6.96−6.91 (2H, m), 6.88−6.84 (2H, m), 6.72 (1H, d, J = 8.4 Hz), 6.53 (1H, d, J = 2.4 Hz), 6.42 (1H, dd, J = 8.4, 2.4 Hz), 5.95 (2H, s), 3.79 (3H, s).

*6-(4-Methoxyphenoxy)quinoline (**10e**).* Following the general procedure, anisole **1e** (54 μL, 0.50 mmol) was converted into **10e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 5% diethyl ether/light petroleum ether to 35% diethyl ether in light petroleum ether afforded the product as a gray powder (60 mg in the first run and 65 mg in the second run, 48% and 52% yield, respectively); analytical TLC on silica gel, 1:3 diethyl ether/petroleum ether, R_f = 0.21. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 46−47 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.80 (1H, dd, J = 4.2, 1.7 Hz), 8.06 (1H, d, J = 9.2 Hz), 7.97−7.94 (1H, m), 7.47 (1H, dd, J = 9.2, 2.7 Hz), 7.33 (1H, dd, J = 8.3, 4.2 Hz), 7.09 (1H, d, J = 2.7 Hz), 7.08−7.04 (2H, m), 6.96−6.91 (2H, m), 3.83 (3H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 157.0, 156.5, 149.6, 148.9, 145.0, 135.1, 131.4, 129.2, 122.7, 121.6, 121.5, 115.2, 111.2, 55.8; HRMS-ESI (m/z) calcd for $C_{16}H_{14}NO_2$ $[M + H]^+$ 252.1025, found 252.1025.

*2-(4-Methoxyphenoxy)-1,3-dimethylbenzene (**11e**).*[29] Following the general procedure, anisole **1e** (54 μL, 0.50 mmol) was converted into **11e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% light petroleum ether to 15% EtOAc in light petroleum ether afforded product as a white powder (68 mg in the first run and 63 mg in the second run, 60% and 55% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f = 0.50. Pure material was obtained by crystallization from petroleum ether: mp 43−45 °C; ^1H NMR (300 MHz, $CDCl_3$, ppm) 7.11−7.00 (3H, m), 6.82−6.76 (2H, m), 6.71−6.65 (2H, m), 3.76 (3H, s), 2.13 (6H, s).

*1,3-Difluoro-2-(4-methoxyphenoxy)benzene (**12e**).* Following the general procedure, anisole **1e** (54 μL, 0.50 mmol) was converted into **12e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% light petroleum ether to 15% EtOAc in light petroleum ether afforded product as a

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colorless oil (45 mg in the first run and 41 mg in the second run, 38% and 35% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether: R_f = 0.38; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.12 (1H, ddt, J = 9.2, 7.7, 5.8 Hz), 7.03−6.95 (2H, m), 6.93−6.88 (2H, m), 6.85−6.80 (2H, m), 3.77 (3H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 156.6 (dd, J = 251.1, 4.6 Hz), 155.4, 152.1, 132.4 (t, J = 14.8 Hz), 124.9 (t, J = 9.1 Hz), 116.5, 114.8, 112.6 (dd, J = 16.7, 5.6 Hz), 55.8. Anal. Calcd for $C_{13}H_{10}O_2F_2$: C, 66.10; H, 4.27. Found: C, 66.44; H, 4.49.

*1-(4-Methoxyphenoxy)-2-prop-2-en-1-ylbenzene (**13e**).*[29] Following the general procedure, anisole **1e** (54 μL, 0.50 mmol) was converted into **13e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% light petroleum ether to 15% EtOAc in light petroleum ether afforded product as a colorless oil (78 mg in the first run and 75 mg in the second run, 65% and 63% yield, respectively): analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f = 0.50; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.24 (1H, dd, J = 7.4, 1.8 Hz), 7.14 (1H, ddd, J = 8.0, 7.5, 1.8 Hz), 7.03 (1H, ddd, J = 7.5, 7.4, 1.1 Hz), 6.93−6.84 (4H, m), 6.79 (1H, dd, J = 8.0, 1.1 Hz), 6.00 (1H, ddt, J = 16.9, 10.2, 6.6 Hz), 5.12−5.03 (2H, m), 3.80 (3H, s), 3.45 (2H, d, J = 6.6 Hz).

*N,N-Diethyl-2-(4-methoxyphenoxy)benzamide (**14e**).*[30] Following the general procedure, anisole **1e** (54 μL, 0.50 mmol) was converted into **14e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% CH_2Cl_2 to 15% diethyl ether in CH_2Cl_2 afforded product as a white powder (79 mg in the first run and 70 mg in the second run, 53% and 47% yield, respectively); analytical TLC on silica gel, 1:10 diethyl ether/CH_2Cl_2, R_f = 0.32. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 62−63 °C; ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 7.36−7.25 (2H, m), 7.12 (1H, td, J = 7.4, 0.9 Hz), 6.99−6.92 (4H, m), 6.78 (1H, dd, J = 8.3, 0.7 Hz), 3.74 (3H, s), 3.54−3.33 (2H, m), 3.18 (2H, q, J = 7.0 Hz), 1.07 (3H, t, J = 7.1 Hz), 1.01 (3H, t, J = 7.1 Hz).

*tert-Butyl [4-(4-Methoxyphenoxy)phenyl]carbamate (**15e**).* Following the general procedure, anisole **1e** (54 μL, 0.50 mmol) was converted into **15e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 10% EtOAc in light petroleum ether to 35% EtOAc in light petroleum ether afforded product as a white powder (99 mg in the first run and 112 mg in the second run, 63% and 71% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, R_f = 0.17. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 124−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.33−7.26 (2H, m), 6.96−6.91 (2H, m), 6.92−6.88 (2H, m), 6.88−6.83 (2H, m), 6.44 (1H, s), 3.79 (3H, s), 1.51 (9H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 155.7, 154.0, 153.1, 151.0, 133.4, 120.5, 120.2, 118.8, 114.9, 80.6, 55.8, 28.5. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.57; H, 6.72; N, 4.37.

*[3-(4-Methoxyphenoxy)phenyl]methanol (**16e**).*[31] Following the general procedure anisole **1e** (54 μL, 0.50 mmol) was converted into **16e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 5% diethyl ether in light petroleum ether to 35% diethyl ether in light petroleum ether afforded product as a pale yellow oil (64 mg in the first run and 60 mg in the second run, 56% and 52% yield, respectively): analytical TLC on silica gel, 1:3 diethyl ether/petroleum ether, R_f = 0.33; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.32−7.26 (1H, m), 7.06−7.02 (1H, m), 7.01−6.93 (3H, m), 6.92−6.84 (3H, m), 4.65 (2H, d, J = 5.6 Hz), 3.81 (3H, s), 1.64 (1H, t, J = 5.6 Hz).

*4-(4-Methoxyphenoxy)benzaldehyde (**17e**).*[32] Following the general procedure, anisole **1e** (54 μL, 0.50 mmol) was converted into **17e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 10% EtOAc in light petroleum ether to 35% EtOAc in light petroleum ether afforded product as a pale yellow powder (82 mg in the first run and 88 mg in the second run, 72% and 77% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, R_f = 0.17. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 60−61 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 9.91 (1H, s), 7.85−7.79 (2H, m), 7.06−6.98 (4H, m), 6.97−6.90 (2H, m), 3.83 (3H, s).

*2-(4-Methoxyphenoxy)pyridine (**18e**).*[27] Following the general procedure, anisole **1e** (54 μL, 0.50 mmol) was converted into **18e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 10% diethyl ether in CH_2Cl_2 to 60% diethyl ether in CH_2Cl_2M afforded product as a gray powder (69 mg in the first run and 65 mg in the second run, 69% and 65% yield, respectively); analytical TLC on silica gel, 1:1 diethyl ether/CH_2Cl_2, R_f = 0.29. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 111−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.37 (1H, ddd, J = 9.2, 6.6, 2.1 Hz), 7.33−7.27 (3H, m), 7.02−6.96 (2H, m), 6.67−6.61 (1H, m), 6.21 (1H, td, J = 6.7, 1.3 Hz), 3.84 (3H, s).

*3-Chloro-5-(4-methoxyphenoxy)pyridine (**19e**).* Following the general procedure, anisole **1e** (54 μL, 0.50 mmol) was converted into **19e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 10% EtOAc in light petroleum ether to 35% EtOAc in light petroleum ether afforded product as a white powder (60 mg in the first run and 65 mg in the second run, 51% and 55% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, R_f = 0.25. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 54−55 °C; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 8.35 (1H, d, J = 2.0 Hz), 8.27 (1H, d, J = 2.5 Hz), 7.42 (1H, dd, J = 2.5, 2.3 Hz), 7.14−7.11 (2H, m), 7.02−6.99 (2H, m), 3.77 (3H, s); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6, ppm) δ 156.4, 155.0, 148.0, 142.0, 138.1, 131.2, 123.7, 121.1, 115.4, 55.4; HRMS-ESI (m/z) calcd for $C_{12}H_{11}NO_2Cl$ $[M + H]^+$ 236.0478, found 236.0483.

*1-Bromo-4-(4-methylphenoxy)benzene (**4a**).*[33] Following the general procedure, toluene **1a** (53 μL, 0.50 mmol) was converted into **4a**. Purification of the crude product by column chromatography (Biotage M+12) using light petroleum ether as a mobile phase afforded product as a white powder (87 mg in the first run and 78 mg in the second run, 66% and 59% yield, respectively); analytical TLC on silica gel, light petroleum ether, R_f = 0.38. Pure material was obtained by crystallization from petroleum ether: mp 65−66 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.44−7.37 (2H, m), 7.18−7.12 (2H, m), 6.94−6.88 (2H, m), 6.88−6.82 (2H, m), 2.34 (3H, s).

*4-(4-Bromophenoxy)-1,2-dimethylbenzene (**4b**).* Following the general procedure, o-xylene **1b** (60 μL, 0.50 mmol) was converted into **4b**. Purification of the crude product by column chromatography (Biotage M+12) using light petroleum ether as a mobile phase afforded product as a colorless oil (96 mg in the first run and 90 mg in the second run, 69% and 65% yield, respectively): analytical TLC on silica gel, light petroleum ether, R_f = 0.32; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.43−7.38 (2H, m), 7.10 (1H, d, J = 8.2 Hz), 6.88−6.83 (2H, m), 6.81 (1H, d, J = 2.6 Hz), 6.75 (1H, dd, J = 8.2, 2.6 Hz), 2.25−2.24 (6H, m); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 157.3, 154.5, 138.5, 132.7, 132.3, 130.9, 120.7, 120.0, 116.7, 115.1, 20.1, 19.2. Anal. Calcd for $C_{14}H_{13}OBr$: C, 60.67; H, 4.73. Found: C, 60.62; H, 4.76.

*1-(4-Bromophenoxy)-2,4-dimethylbenzene(**4c**).* Following the general procedure, m-xylene **1c** (62 μL, 0.50 mmol) was converted into **4c**. Purification of the crude product by column chromatography (Biotage M+12) using light petroleum ether as a mobile phase afforded product as a colorless oil (103 mg in the first run and 96 mg in the second run, 74% and 69% yield, respectively): analytical TLC on silica gel, light petroleum ether, R_f = 0.42; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.39−7.35 (2H, m), 7.08−7.06 (1H, m), 7.01−6.97 (1H, m), 6.84−6.80 (1H, m), 6.78−6.73 (2H, m), 2.33 (3H, s), 2.16 (3H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 157.7, 151.6, 134.3, 132.6, 132.4, 130.1, 128.0, 120.4, 118.5, 114.3, 20.9, 16.2. Anal. Calcd for $C_{14}H_{13}OBr$: C, 60.67; H, 4.73. Found: C, 61.03; H, 4.81.

*4-Bromophenyl 5,6,7,8-Tetrahydronaphthalen-2-yl Ether (**4d**).* Following the general procedure, tetraline **1d** (68 μL, 0.50 mmol) was converted into **4d**. Purification of the crude product by column chromatography (Biotage M+12) using light petroleum ether as a mobile phase afforded product as a colorless oil (70 mg in the first run and 83 mg in the second run, 46% and 55% yield, respectively):

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analytical TLC on silica gel, light petroleum ether, R_f = 0.29; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.42−7.38 (2H, m), 7.04 (1H, d, J = 8.2 Hz), 6.89−6.84 (2H, m), 6.75 (1H, dd, J = 8.2, 2.6 Hz), 6.72 (1H, d, J = 2.6 Hz), 2.78−2.71 (1H, m), 1.82−1.77 (4H, m); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 157.3, 154.2 139.0, 132.9, 132.7, 130.5, 120.1, 119.6, 116.8, 115.1, 29.7, 28.9, 23.4, 23.1. Anal. Calcd for $C_{16}H_{15}OBr$: C, 63.38; H, 4.99. Found: C, 63.42; H, 4.97.

*1-Bromo-4-[4-(prop-2-en-1-yloxy)phenoxy]benzene (**4f**).*[34] Following the general procedure, *O*-allyl ether **1f** (68 μL, 0.50 mmol) was converted into **4f**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 5% EtOAc in light petroleum ether to 25% EtOAc in light petroleum ether afforded product as a white powder (109 mg in the first run and 111 mg in the second run, 72% and 73% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, R_f = 0.42. Pure material was obtained by crystallization from petroleum ether: mp 58−59 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.43−7.35 (2H, m), 6.99−6.87 (4H, m), 6.86−6.78 (2H, m), 6.06 (1H, ddt, J = 17.2, 10.5, 5.3 Hz), 5.42 (1H, dq, J = 17.3, 1.6 Hz), 5.30 (1H, dq, J = 10.5, 1.4 Hz), 4.53 (2H, dt, J = 5.3, 1.5 Hz).

*1-(Benzyloxy)-4-(4-bromophenoxy)benzene (**4g**).*[35] Following the general procedure, *O*-benzyl ether **1g** (92 mg, 0.50 mmol) was converted into **4g**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 5% EtOAc in light petroleum ether to 25% EtOAc in light petroleum ether afforded product as a white powder (135 mg in the first run and 140 mg in the second run, 76% and 79% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, R_f = 0.35. Pure material was obtained by crystallization from petroleum ether: mp 109−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.46−7.33 (7H, m), 6.96 (4H, s), 6.86−6.80 (2H, m), 5.06 (2H, s).

*[4-(4-Bromophenoxy)phenoxy](tert-butyl)dimethylsilane (**4h**).* Following the general procedure, *O*-TBDMS phenol **1h**[36] (105 mg, 0.50 mmol) was converted into **4h**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% light petroleum ether to 10% EtOAc in light petroleum ether afforded product as a colorless oil (125 mg in the first run and 131 mg in the second run, 66% and 69% yield, respectively): analytical TLC on silica gel, light petroleum ether, R_f = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.41−7.37 (2H, m), 6.91−6.87 (2H, m), 6.84−6.80 (4H, m), 0.99 (9H, s), 0.21 (6H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 157.8, 152.2, 150.3, 132.6, 121.2, 120.8, 119.5, 114.9, 25.8, 18.3, −4.3. Anal. Calcd for $C_{18}H_{23}O_2BrSi$: C, 56.99; H, 6.11. Found: C, 56.98; H, 6.10.

*2-Bromo-4-(4-bromophenoxy)-1-methoxybenzene (**4i**).* Following the general procedure, 2-bromoanisole **1i** (62 μL, 0.50 mmol) was converted into **4i**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% light petroleum ether to 10% EtOAc in light petroleum ether afforded product as a white powder (125 mg in the first run and 109 mg in the second run, 70% and 61% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, R_f = 0.50. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 69−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.44−7.39 (2H, m), 7.25 (1H, d, J = 2.8 Hz), 6.96 (1H, dd, J = 8.9, 2.8 Hz), 6.88 (1H, d, J = 8.9 Hz), 6.86−6.81 (2H, m), 3.89 (3H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 157.2, 152.8, 150.2, 132.8, 124.9, 119.7, 119.5, 115.6, 112.7, 112.2, 56.8. Anal. Calcd for $C_{13}H_{10}O_2Br_2$: C, 43.61; H, 2.82. Found: C, 43.54; H, 2.72.

*5-(4-Bromophenoxy)-2,3-dihydro-1-benzofuran (**4j**).* Following the general procedure, dihydrobenzofuran **1j** (56 μL, 0.50 mmol) was converted into **4j**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% light petroleum ether to 10% EtOAc in light petroleum ether afforded product as a white powder (70 mg in the first run and 95 mg in the second run, 48% and 65% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, R_f = 0.42. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 54−55 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.40−7.36 (2H, m), 6.90−6.87 (1H, m), 6.83−6.79 (2H, m), 6.79−6.76 (1H, m), 6.74 (1H, d, J = 8.5 Hz), 4.59 (2H, t, J = 8.7 Hz), 3.20 (2H, t, J = 8.7 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 158.3, 156.8, 149.7, 132.6, 128.7, 119.7, 119.1, 117.3, 114.6, 109.8, 71.7, 30.2. Anal. Calcd for $C_{14}H_{11}O_2Br$: C, 57.76; H, 3.81. Found: C, 57.59; H, 3.72.

*2-[5-(4-Bromophenoxy)-2-methoxyphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**4k**).* Following the general procedure, pinacolyl boronate **1k**[37] (117 mg, 0.50 mmol) was converted into **4k**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 5% EtOAc in light petroleum ether to 25% EtOAc in light petroleum ether afforded product as a white powder (142 mg in the first run and 122 mg in the second run, 70% and 60% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, R_f = 0.10. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 133−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.40−7.33 (3H, m), 7.05 (1H, dd, J = 8.9, 3.1 Hz), 6.84 (1H, d, J = 8.9 Hz), 6.82−6.77 (2H, m), 3.83 (3H, s), 1.34 (12H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 161.0, 158.2, 149.0, 132.6, 128.2, 124.1, 119.0, 114.5, 112.0, 83.9, 56.6, 25.0. Anal. Calcd for $C_{19}H_{22}O_4BBr$: C, 56.33; H, 5.47. Found: C, 56.37; H, 5.45.

*1-(4-Bromophenoxy)-2,4-dimethoxybenzene (**4l**).* Following the general procedure, resorcinol dimethyl ether **1l** (65 μL, 0.50 mmol) was converted into **4l**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% light petroleum ether to 20% EtOAc in light petroleum ether afforded product as a colorless oil (80 mg in the first run and 88 mg in the second run, 52% and 57% yield, respectively): analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, R_f = 0.33; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.37−7.32 (2H, m), 6.95 (1H, d, J = 8.7 Hz), 6.78−6.74 (2H, m), 6.58 (1H, d, J = 2.8 Hz), 6.46 (1H, dd, J = 8.7, 2.8 Hz), 3.82 (3H, s), 3.77 (3H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 158.3, 157.8, 152.6, 137.8, 132.4, 122.6, 117.8, 114.1, 104.4, 100.8, 56.1, 55.8. Anal. Calcd for $C_{14}H_{13}O_3Br$: C, 54.39; H, 4.24. Found: C, 54.24; H, 4.18.

*2-(4-Bromophenoxy)-3,5-dimethoxy-N-methylbenzamide (**4m**).* Following the general procedure, 3,5-dimethoxy-*N*-methylbenzamide (**1m**)[8a] (97 mg, 0.50 mmol) was converted into **4m**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% CH_2Cl_2 to 10% diethyl ether in CH_2Cl_2 afforded product as a white powder (51 mg in the first run and 49 mg in the second run, 28% and 27% yield, respectively); analytical TLC on silica gel, 1:10 diethyl ether/CH_2Cl_2, R_f = 0.31. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 116−117 °C; IR (film, cm^{-1}) 3324 (N−H), 1638 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.38−7.32 (2H, m), 7.23 (1H, d, J = 3.0 Hz), 7.21−7.15 (1H, m), 6.74−6.69 (2H, m), 6.65 (1H, d, J = 3.0 Hz), 3.86 (3H, s), 3.68 (3H, s), 2.88 (3H, d, J = 4.9 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 165.2, 157.6, 157.1, 153.0, 135.1, 132.7, 128.6, 117.0, 115.1, 104.8, 104.2, 56.3, 55.9, 27.0; HRMS-ESI (m/z) calcd for $C_{16}H_{17}NO_4Br$ $[M + H]^+$ 366.0341, found 366.0354.

*3-Methyl-2-(4-nitrophenoxy)thiophene (**4n**).* Following the general procedurem methylthiophene **1n** (48 μL, 0.50 mmol) was converted into **4n**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 100% light petroleum ether to 15% EtOAc in light petroleum ether afforded product as a pale yellow powder (59 mg in the first run and 59 mg in the second run, 50% and 50% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, R_f = 0.32. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 69−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.23−8.19 (2H, m), 7.08−7.03 (2H, m), 6.90 (1H, d, J = 5.9 Hz), 6.77 (1H, d, J = 5.9 Hz), 2.02 (3H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 163.8, 150.4, 143.1, 128.1, 126.1, 125.6, 117.5, 115.9, 11.8; HRMS-ESI (m/z) calcd for $C_{11}H_{10}NO_3S$ $[M + H]^+$ 236.0381, found 236.0388.

*Ethyl 5-Bromo-1-methyl-3-(4-nitrophenoxy)-1H-indole-2-carboxylate (**4o**).* Following the general procedure, indole **1o**[8a] (141 mg, 0.50 mmol) was converted into **4o**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 5% EtOAc in light petroleum ether to 25% EtOAc in light petroleum ether afforded product as a pale yellow powder (140 mg in the first run

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and 155 mg in the second run, 67% and 74% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, R_f = 0.17. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 151−152 °C; IR (film, cm^{-1}) 1717 (C═O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.22−8.16 (2H, m), 7.61 (1H, dd, J = 1.9, 0.4 Hz), 7.48 (1H, dd, J = 9.0, 1.9 Hz), 7.33 (1H, dd, J = 9.0, 0.4 Hz), 7.03−6.97 (2H, m), 4.20 (2H, q, J = 7.1 Hz), 4.07 (3H, s), 1.05 (3H, t, J = 7.1 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 164.1, 160.7, 142.7, 135.9, 135.3, 129.5, 126.0, 121.6, 120.7, 119.2, 115.5, 114.5, 112.3, 61.1, 32.2, 14.0. Anal. Calcd for $C_{18}H_{15}N_2O_5Br$: C, 51.57; H, 3.61; N, 6.68. Found: C, 51.36; H, 3.52; N, 6.55.

*5-Bromo-1-methyl-3-(4-nitrophenoxy)-1H-indole-2-carbonitrile (**4p**).* Following the general procedure, 2-cyanoindole **1p**[38] (118 mg, 0.50 mmol) was converted into **4p**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc in light petroleum ether to 45% EtOAc in light petroleum ether afforded product as a pale yellow powder (100 mg in the first run and 95 mg in the second run, 54% and 51% yield, respectively); analytical TLC on silica gel, 1:5 EtOAc/light petroleum ether, R_f = 0.16. Pure material was obtained by crystallization from EtOAc/petroleum ether: mp 202−203 °C; IR (film, cm^{-1}) 2220 (C≡N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.25−8.22 (2H, m), 7.53 (1H, dd, J = 8.9, 1.9 Hz), 7.48 (1H, dd, J = 1.9, 0.6 Hz), 7.29 (1H, dd, J = 9.0, 0.5 Hz), 7.12−7.09 (2H, m), 3.90 (3H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 162.4, 143.6, 139.6, 135.0, 130.4, 126.3, 121.7, 119.6, 116.3, 115.3, 112.4, 110.7, 103.1, 32.1. Anal. Calcd for $C_{16}H_{10}N_3O_3Br$: C, 51.64; H, 2.71; N, 11.29. Found: C, 51.55; H, 2.72; N, 10.96.

*Methyl 1-Methyl-5-(4-nitrophenoxy)-1H-pyrrole-2-carboxylate (**4q**).* Following the general procedure, methyl-1*H*-pyrrole **1q** (70 mg, 0.50 mmol) was converted into **4q**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 10% EtOAc in light petroleum ether to 30% EtOAc in light petroleum ether afforded product as a pale yellow powder (68 mg in the first run and 68 mg in the second run, 49% and 49% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, R_f = 0.16. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 135−136 °C; IR (film, cm^{-1}) 1716 (C═O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.19−8.15 (2H, m), 7.09−7.05 (2H, m), 6.69−6.67 (2H, m), 3.94 (3H, s), 3.82 (3H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 164.3, 161.3, 142.6, 139.1, 126.0, 120.7, 119.7, 116.0, 109.1, 51.5, 37.2; HRMS-ESI (m/z) calcd for $C_{13}H_{13}N_2O_5$ $[M + H]^+$ 277.0824, found 277.0819.

*Methyl 1-(2-Bromobenzyl)-2,5-dimethyl-4-(4-nitrophenoxy)-1H-pyrrole-3-carboxylate (**4r**).* Following the general procedure, 1*H*-pyrrole **1r**[39] (161 mg, 0.50 mmol) was converted into **4r**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 10% EtOAc in light petroleum ether to 30% EtOAc in light petroleum ether afforded product as a pale yellow powder (92 mg in the first run and 106 mg in the second run, 40% and 46% yield, respectively); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, R_f = 0.16. Pure material was obtained by crystallization from diethyl ether/petroleum ether: mp 159−160 °C; IR (film, cm^{-1}) 1700 (C═O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.21−8.16 (2H, m), 7.61 (1H, dd, J = 7.8, 1.3 Hz), 7.26 (1H, td, J = 7.6, 1.2 Hz), 7.19 (1H, td, J = 7.7, 1.7 Hz), 7.02−6.97 (2H, m), 6.37−6.33 (1H, m), 5.08 (2H, s), 3.57 (3H, s), 2.46 (3H, s), 1.96 (3H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, ppm) δ 164.9, 164.3, 142.2, 135.53, 135.47, 134.3, 133.1, 129.5, 128.4, 126.4, 125.9, 121.7, 119.1, 115.3, 104.6, 50.9, 47.7, 11.3, 8.2; HRMS-ESI (m/z) calcd for $C_{21}H_{20}N_2O_5Br$ $[M + H]^+$ 459.0556, found 459.0551.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02728.

^1H and ^{13}C spectra (PDF)

X-ray crystallographic data for λ^3-iodane **20** (CIF)

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Notes

The authors declare no competing financial interest.

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Ar savu parakstu apliecinu, ka pētījums veikts patstāvīgi, izmantoti tikai tajā norādītie informācijas avoti un iesniegtā darba elektroniskā kopija atbilst izdrukai.

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