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Aleksandrs Čižikovs

JAUNU KOBALTA KATALIZĒTU METOŽU IZSTRĀDE HETEROCIKLU IEGŪŠANAI

Promocijas darbs

DEVELOPMENT OF NOVEL METHODS FOR THE SYNTHESIS OF HETEROCYCLES USING COBALT CATALYSIS

Doctoral Thesis

RTU Izdevniecība
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RĪGAS TEHNISKĀ UNIVERSITĀTE
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Doctoral Thesis

Zinātniskā vadītāja
docente *Dr. chem.*
LIENE GRIGORJEVA

Scientific supervisor
Docent Dr. chem.
LIENE GRIGORJEVA

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PROMOCIJAS DARBS IZVIRZĪTS ZINĀTNES DOKTORA GRĀDA IEGŪŠANAI RĪGAS TEHNISKAJĀ UNIVERSITĀTĒ

Promocijas darbs zinātnes doktora (*Ph. D.*) grāda iegūšanai tiek publiski aizstāvēts 2025. gada 4. decembrī plkst. 14.00 Rīgas Tehniskās universitātes Dabaszinātņu un tehnoloģiju fakultātē, Rīgā, Paula Valdena ielā 3, 272. auditorijā.

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APSTIPRINĀJUMS

Apstiprinu, ka esmu izstrādājis šo promocijas darbu, kas iesniegts izskatīšanai Rīgas Tehniskajā universitātē zinātnes doktora (*Ph. D.*) grāda iegūšanai. Promocijas darbs zinātniskā grāda iegūšanai nav iesniegts nevienā citā universitātē.

Aleksandrs Čižikovs ……………………………. (paraksts)
Datums: ………………………

Promocijas darbs sagatavots kā tematiski vienota zinātnisko publikāciju kopa. Tas ietver kopsavilkumu, trīs publikācijas, divus apskatrakstus un vienu grāmatas nodaļas. Publikācijas uzrakstītas angļu valodā, to kopējais apjoms, ieskaitot elektroniski pieejamo informāciju, ir 501 lpp.

SATURS/CONTENTS

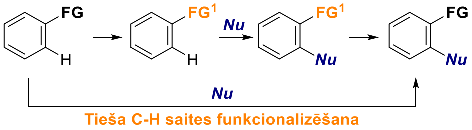
SAĪSINĀJUMI/ABBREVIATIONS AND ACRONYMS

µA	mikroampērs/microampere
Å	angstrēms/angstrom
Ac	acetil-/acetyl
AIDS	iegūta imūndeficīta sindroms/acquired immune deficiency syndrome
AIMS	augstas izšķirtspējas masas spektrometrija
Boc	*terc*-butiloksikarbonil-/*tert*-butyloxycarbonyl
brsm	rēķinot pēc atgūtās izejvielas daudzuma/based on the recovered starting material
CAN	cērija ammonija nitrāts/ceric ammonium nitrate
CV	cikliskā voltametrija/cyclic voltammetry
DBU	1,8-diazabiciklo[5.4.0]undec-7-ēns/1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dihloretāns/1,2-dichloroethane
DFT	blīvuma funkcionāļa teorija/density-functional theory
DIAD	diizopropilazodikarboksilāts/diisopropylazodicarboxylate
DIPEA	diisopropiletilamīns/diisopropylethylamine
dpm	dipivaloilmetāns/dipivaloylmethane
EDCi	1-etil-3-(3-dimetilaminopropil)karbodiimīds/1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	etil-/ethyl
FG	funkcionālā grupa/functional group
HIV	cilvēka imūndeficīta vīruss/human immunodeficiency virus
HOBt	1H-1,2,3-benzotriazol-1-ols/1H-1,2,3-benzotriazol-1-ol
HRMS	high resolution mass spectrometry
IBSA	izobutānskābes anhidrīds/isobutyric acid anhydride
IBX	2-jodoksibenzoskābe/2-iodoxybenzoic acid
ist. t.	istabas temperatūra
KMR	kodolu magnētiskā rezonanse
Me	metil-/methyl
mV/s	millivolti sekundē/millivolt per second
NFSI	*N*-fluorobenzolsulfonimīds/*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
Nu	nukleofīls/nucleophile
PA	pikolīnamīds/picolinamide
Phth	ftaloil-/phthaloyl
Piv	pivaloil-/pivaloyl
Q	8-aminohinolīns/8-aminoquinoline
rt	room temperature
TBS	*terc*-butildimetilsilil-/*tert*-butyldimethylsilyl
*t*Bu	*terc*-butil-/*tert*-butyl
TMS	trimetilsilil-/trimethylsilyl

PROMOCIJAS DARBA VISPĀRĒJS RAKSTUROJUMS

Tēmas aktualitāte

Organiskās sintētiskās ķīmijas galvenais mērķis ir konstruēt sarežģītākas struktūras no vienkāršām molekulām. Klasiskā organiskā sintēze bieži vien balstās uz funkcionālo grupu manipulācijām – reakciju virkni, lai iegūtu vēlamos produktus. Termins “C-H saites funkcionalizēšana” organiskajā ķīmijā tiek lietots, lai aprakstītu ķīmisku procesu, kurā izejvielā esošā C-H saite tiek uzšķelta un aizvietota ar C-C, C-N, C-S, C-Hal vai kādu citu saiti (1. att.). Bieži vien šāda tipa transformāciju nevar realizēt nepietiekama C-H saites skābuma vai zemās reaģētspējas dēļ. Lai risinātu šo problēmu, mūsdienās ir ieviesta jauna pieeja C-H saites funkcionalizēšanai, kurā tiek izmantoti pārejas metāli. Patlaban pārejas metālu katalizēta C-H saites aktivēšana un funkcionalizēšana ir neatņemama organiskās sintēzes sastāvdaļa, un tai ir būtiska ietekme jaunu zāļvielu atklāšanas jomā, materiālzinātnē, kā arī dažādu dabas produktu sintēzē.[1–3]



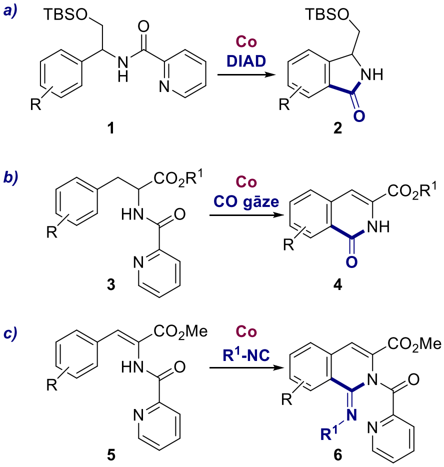
1. att. Vispārīgā shēma C-H saites funkcionalizēšanai.

Liela daļa no šāda veida pārejas metālu katalizētajām pārvērtībām ir salīdzinoši viegli realizējamas, izmantojot dārgmetālu (Ru, Rh, Ir, Pd) katalizatorus, turklāt šie metālu katalizatori ir uzrādījuši gan augstu reaģētspēju, gan arī tiem piemīt lieliska selektivitāte. Neskatoties uz šo dārgmetālu augsto reaģētspēju, to izmantošana nav ilgtspējīga un tiek ierobežota, jo tie dabā ir reti sastopami, tiem piemīt zināma toksicitāte, līdz ar to reakciju realizēšana prasa samērā lielas izmaksas.[4]

Kobalts ir 4. perioda IX grupas pārejas metāls ar atomskaitli 27. Kobalts ietilpst vitamīna B12 jeb ciānkobalamīna sastāvā, kas padara to par vienu no svarīgākajiem metāliem dzīvajiem organismiem. Turklāt kobalta savienojumi dažādās oksidēšana pakāpēs bieži tiek lietoti organiskajā sintēzē kā reakciju katalizatori.[2]

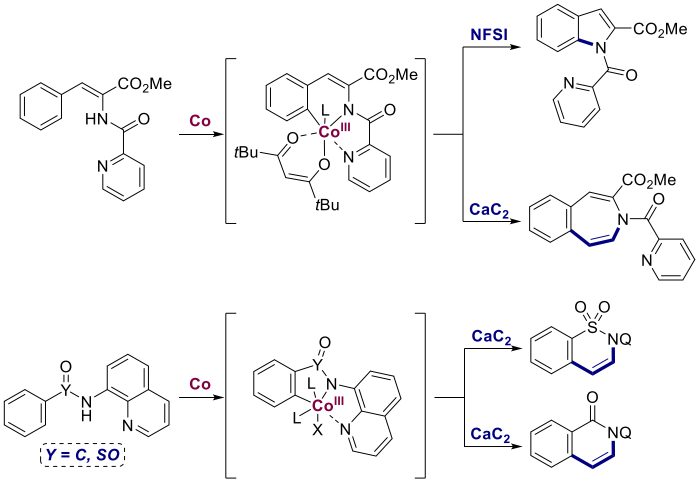
Kobalta katalizētas C-H saites aktivēšanas un funkcionalizēšanas reakcijas var iedalīt divās kategorijās – zemas valences kobalta katalīze, kur kobaltam ir raksturīgas oksidēšanas pakāpes 0 un +1, un augstas valences kobalta katalīze, kur lietotajiem kobalta katalizatoriem ir raksturīga oksidēšanas pakāpe +3, ko iegūst no Co(III) vai Co(II) sāļiem reakcijas vidē oksidējošos apstākļos.[5, 6] Vēsturiski kobalta katalizētas reakcijas piesaistīja uzmanību 1941. gadā, kad *Kharasch* un *Fields* grupa publicēja pētījumu, kurā tika demonstrēts, ka Griņjāra reaģenti spēj dimerizēties kobalta dihlorīda klātbūtnē.[7] Savukārt 1955. gadā japāņu ķīmiķis *Murahashi* bija pirmais, kas izstrādāja kobalta katalizētu C-H saites funkcionalizēšanas reakciju, kā reakcijas katalizatoru izmantojot zemas valences dikobalta oktakarbonilu.[8] Kopš kobalta katalizētu C-H saites funkcionalizēšanas reakciju ieviešanas būtiskākie panākumi tika gūti, izmantojot zemas valences kobalta katalizatorus. Tomēr aptuveni no 2013.–2014. gada sāka pieaugt interese par augstas valences Co(III) un tā prekursora Co(II) sāļu izmantošanu. Turpmākajos gados šāda tipa katalīze kļuva par nozīmīgu pētniecības virzienu. Mūsdienās tiek radītas jaunas metodes, kurās augstas valences kobalta katalīzi apvieno ar zaļās ķīmijas pamatprincipiem – aizvieto metālu oksidētājus ar elektroenerģiju,[9] lieto lētus reaģentu prekursorus indīgo gāzu ģenerēšanai,[10, 11] apvieno foto-redoks reakcijas ar pārejas metālu ķīmiju,[12] izmanto viegli nošķeļamas virzošās grupas[13] u. c.

Iepriekš veiktajos pētījumos promocijas darba autora grupai izdevies izstrādāt efektīvas metodes kobalta katalizētai aminospirtu un aminoskābju C-H saites funkcionalizēšanai (2. att.). Tika atklāts, ka aizvietotus fenilglicinolus **1** var pārvērst par izoindolinoniem **2** karbonilēšanas apstākļos, kā tvāna gāzes avotu izmantojot DIAD (2. a. att.).[10] Tad, turpinot pētījumu par aminoskābju C-H saites funkcionalizēšanu, tika atklātas fenilalanīnu atvasinājumu **3** un **5** karbonilēšanas (2. b. att.)[14] un imīnēšanas (2. c. att.)[15] reakcijas, iegūstot izohinolīna **4** un imīnoizohinolīna **6** atvasinājumus. Interesanti, ka karbonilēšanas reakciju apstākļos pikolīnamīda virzošā grupa tika nošķelta *in situ.*



2. att. Iepriekšējie pētījumi kobalta katalizētai heterociklu **2**, **4**, **6** sintēzei.

Jaunu metožu izstrāde heterociklisko savienojumu – gan jaunu, gan jau zināmu – iegūšanai varētu ne tikai veicināt jaunu sintēzes pieeju attīstību, bet arī potenciāli samazināt jau esošo farmaceitisko preparātu ražošanas izmaksas. Šo iemeslu dēļ promocijas darba autora un viņa kolēģu pētījumi ir vērsti uz jaunu kobalta katalizētu C-H saites aktivēšanas un funkcionalizēšanas metožu izstrādi dažādu heterociklisko savienojumu iegūšanai (3. att.). Promocijas darbā izstrādātās metodes balstās augstas valences kobalta katalīzē, kur kā Co(III) prekursors tiek izmantoti Co(II) sāļi kombinācijā ar bidentātu virzošo grupu.



3. att. Dažādu heterociklu atvasinājumu iegūšanas iespējas kobalta katalīzes apstākļos.

Pētījuma mērķis un uzdevumi

Promocijas darba mērķis ir izstrādāt jaunas, praktiskas un ērti izmantojamas metodes kobalta katalizētai C-H saites funkcionalizēšanai. Lai sasniegtu šo mērķi, tika definēti vairāki darba uzdevumi.

1. Iegūt α-amīdoakrilātu, sulfonamīdu un benzamīdu atvasinājumus, kurus potenciāli varētu izmantot kobalta katalizētai C-H saites aktivēšanai un funkcionalizēšanai.
2. Veikt literatūras izpēti un identificēt piemērotos reaģentus, kas varētu piedalīties kobalta katalizētās C-H saites funkcionalizēšanas reakcijās.
3. Veikt reakcijas apstākļu optimizēšanu un substrātu klāsta izpēti, noskaidrojot metodes ierobežojumus. Veikt nepieciešamos eksperimentus, lai noskaidrotu iespējamo reakcijas mehānismu.

Zinātniskā novitāte un galvenie rezultāti

Darbā ir izstrādātas divas jaunas metodes α-amīdoakrilātu atvasinājumu C-H saites funkcionalizēšanai un viena jauna metode sulfonamīdu un benzamīdu C-H saites annulēšanai.

1. Kobalta katalizēta indolu sintēze α-amīdoakrilātu atvasinājumu C-H saites iekšmolekulārā amidēšanā.
2. Kobalta katalizēta 3-benzazepīna atvasinājumu sintēze α-amīdoakrilātu atvasinājumu reakcijā ar kalcija karbīdu.
3. Kobalta katalizēta sulfonamīdu un benzamīdu C-H saites annulēšana ar kalcija karbīdu.

Darba struktūra un apjoms

Promocijas darbs sagatavots kā tematiski vienota zinātnisko publikāciju kopa par kobalta katalizētu C-H saites funkcionalizēšanas metožu izstrādi. Tas ietver metodi indolu sintēzei α-amīdoakrilātu atvasinājumu iekšmolekulārā amidēšanā, 3-benzazepīnu iegūšanas metodi α-amīdoakrilātu atvasinājumu reakcijā ar kalcija karbīdu kā acetilēna gāzes avotu, kā arī metodi sulfonamīdu un benzamīdu atvasinājumu C-H saites annulēšanai ar kalcija karbīdu. Turklāt promocijas darbs ietver arī apskatrakstus par mehānismu pētījumiem.

Darba aprobācija un publikācijas

Promocijas darba galvenie rezultāti apkopoti trīs zinātniskajās oriģinālpublikācijās, divos apskata rakstos, un vienā grāmatas nodaļā. Pētījuma rezultāti prezentēti sešās zinātniskajās konferencēs.

Zinātniskās publikācijas

1. **Cizikovs, A.**, Grigorjeva, L. Cobalt-Catalyzed C-H Annulation of Aryl Sulfonamides and Benzamides with CaC_2 as the Acetylene Source. *Org. Lett.* **2025**, *27*(26), 7070-7074. DOI: 10.1021/acs.orglett.5c01981.
2. **Cizikovs, A.**, Lukasevics, L. T., Zagorska, P. A., Grigorjeva, L. Cobalt-Catalyzed C–H Bond Functionalization: a Personal Account. *Synlett* **2025**, *36*(12), 1659-1668.. DOI:10.1055/s-0043-1775473.
3. **Cizikovs, A.**, Zagorska, P. A., Grigorjeva, L. Synthesis of 3-Benzazepines via Cobalt-Catalyzed C–H Bond Functionalization with CaC_2 as the Acetylene Source. *Org. Lett.* **2024**, *26*, 9536. DOI: 10.1021/acs.orglett.4c03551
4. **Cizikovs, A.**, Basens, E. E., Zagorska, P. A., Kinens, A., Grigorjeva, L. Indole Synthesis by Cobalt-Catalyzed Intramolecular Amidation via the Oxidatively Induced Reductive Elimination Pathway. *ACS Catal.* **2024**, *14*, 1690. DOI:10.1021/acscatal.3c05706
5. **Cizikovs, A.**, Grigorjeva, L. Co(III) Intermediates in Cobalt-Catalyzed, Bidentate Chelation Assisted $C(sp^2)$-H Functionalizations. *Inorganics* **2023**, *11*, 194. DOI:10.3390/inorganics11050194

Grāmatas nodaļas

1. **Cizikovs, A.**, Basens, E.E., Zagorska, P.A., Grigorjeva, L. Diastereoselective C-H Functionalizations. *Comprehensive Chirality, 2nd edition (Ed. J. R. Cossy)*. **2024**, 138. DOI: 10.1016/B978-0-32-390644-9.00101-3.

Zinātniskās konferences un pasākumi, kuros prezentēti darba rezultāti

1. **Cizikovs, A.** Development of Novel Methods for the Synthesis of Heterocycles Using Cobalt Catalysis. *Paul Walden 14th Symposium on Organic Chemistry.* Rīga, Latvija, 25.–26. septembris **2025**.

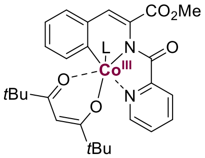
2. **Cizikovs, A.,** Grigorjeva, L. Cobalt-Catalyzed C-H Annulation of Aryl Sulfonamides and Benzamides with CaC_2 as the Acetylene Source. *International Symposium on Synthesis and Catalysis 2025*. Koimbra, Portugāle, 2.–5. septembris **2025**.
3. Pieredzes apmaiņas brauciens uz Hjūstonas Universitāti pie prof. Olafa Dauguļa. Prezentācija: "Cobalt-Catalyzed C-H Bond Functionalization" Hjūstona, ASV, 12.–17. maijs **2025**.
4. **Cizikovs A.,** Zagorska, P. A., Grigorjeva L. Mechanistic Insights Into Cobalt-Catalyzed C-H Bond Functionalization of α-Amidoacrylates. *7th International Symposium on C-H Activation*. IIT Bombay, Mumbaja, Indija, 6.–9. decembris **2024**.
5. **Cizikovs A.,** Zagorska P. A., Grigorjeva L. CaC_2 – an effective acetylene surrogate for the synthesis of benzoazepine derivatives via cobalt catalysis. *Balticum Organicum Syntheticum 2024 (BOS 2024)*. Rīga, Latvija, 7.–10. jūlijs **2024**.
6. **Cizikovs A.,** Basens E. E., Zagorska P. A., Kinens A., Grigorjeva L. Indole Synthesis by Cobalt-Catalyzed Intramolecular Amidation via the Oxidatively Induced Reductive Elimination Pathway. *European Meeting on C-H Activation*. Lisabona, Portugāle, 23.–24. janvāris **2024**.
7. **Cizikovs A.,** Basens E. E., Zagorska P. A., Grigorjeva L. Indole synthesis via $C(sp^2)$–H bond functionalization of amino acids. *Paul Walden 13th Symposium on Organic Chemistry*. Rīga, Latvija, 14.–15. septembris **2023**.
8. **Cizikovs A.,** Basens E. E., Zagorska P. A., Grigorjeva L. The reactivity of $C(sp^2)$–H activated cobalt complexes: a straightforward synthesis of indoles. *International Symposium on Synthesis and Catalysis 2023*. Évora, Portugāle, 5.–8. septembris **2023**.

PROMOCIJAS DARBA GALVENIE REZULTĀTI

1. Kobalta katalizēta indolu sintēze α-amīdoakrilātu iekšmolekulārā amidēšanā

Mūsdienās ir attīstītas dažādas sintētiskās metodes indolu atvasinājumu iegūšanai, tai skaitā Fišera indolu sintēze un pallādija katalizētas ciklizēšanas reakcijas.[16] Lai arī šīs metodes bieži tiek izmantotas, tām ir dažādi ierobežojumi, rodas nevēlami blakusprodukti vai ir nepieciešami dārgi reaģenti. Šo iemeslu dēļ jaunu metožu izstrāde indola atvasinājumu iegūšanai, izmantojot 3d grupas pārejas metālu katalizatorus (Co, Fe, Mn u.c.), ir ļoti vēlama.

Pētot α-amīdoakrilātu karbonilēšanas un iminēšanas reakcijas, iepriekšējos pētījumos no reakcijas apstākļiem ar 4 % iznākumu tika izdalīts C-H aktivētais Co(III) komplekss **7a** (4. att.).[14, 15]

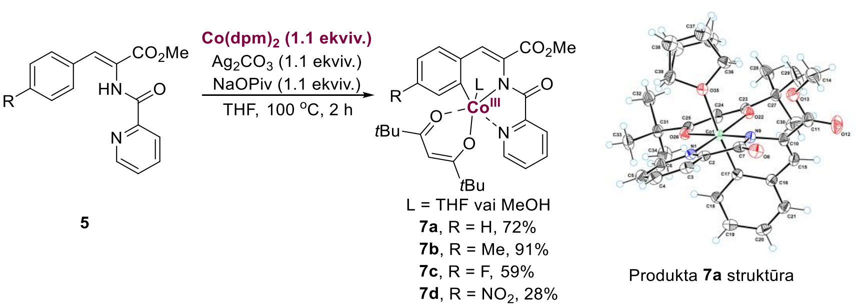


7a

L = CD$_3$OD

4. att. Izolētā kompleksa **7a** struktūra.

Tika plānots izpētīt šī kompleksa reaģētspēju, līdz ar to bija nepieciešams sintezēt šo kompleksu lielākā apjomā. Dažādi aizvietoti Co(III) organiskie kompleksi tika iegūti vienā stadijā no α,β-nepiesātinātām aminoskābēm **5**, izmantojot Co(dpm)$_2$, Ag$_2$CO$_3$ un NaOPiv nelielā pārākumā (5. att.). Kristalizējot kompleksu **7a** no sausā THF, bija iespējams iegūt monokristālus, un pierādīt kompleksa **7a** struktūru ar rentgenstruktūranalīzes palīdzību.

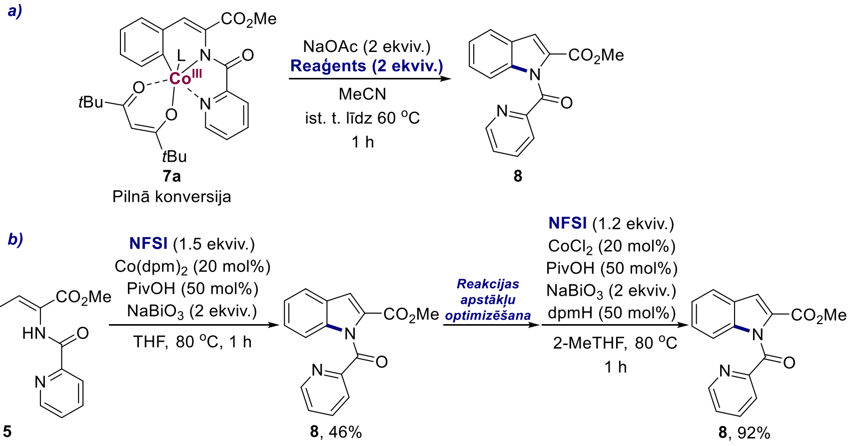


Produkta **7a** struktūra

5. att. Co(III) kompleksu **7a-d** sintēze.

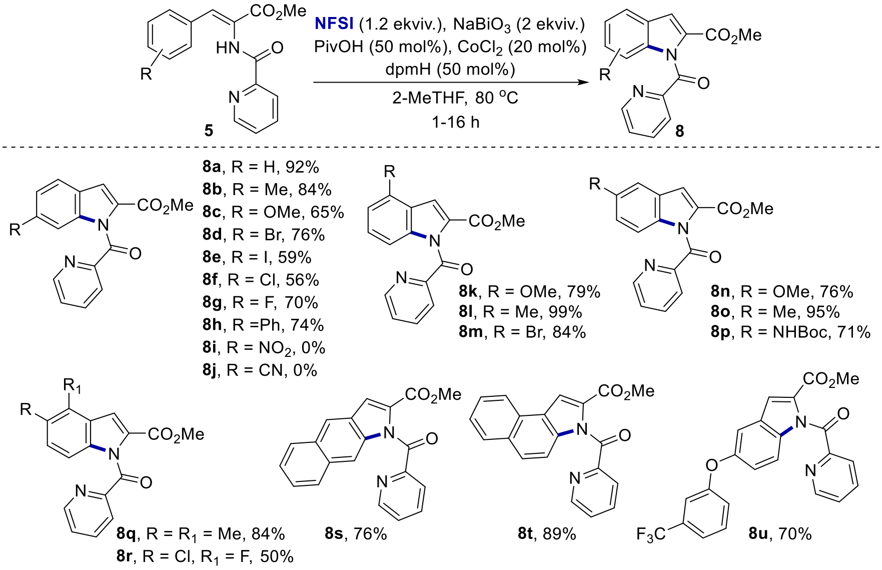
No iegūto produktu **7a-d** iznākumiem varēja secināt, ka C-H saites aktivēšanas iznākums līdzīgiem substrātiem lielā mērā ir atkarīgs no elektroniskiem efektiem, jo elektroniem bagātāks substrāts **5b** (satur metilgrupu) reaģēja labāk nekā elektroniem nabadzīgāks substrāts **5d** (satur nitrogrupu).

Tālāk tika veikti kompleksa **7a** reaģētspējas pētījumi (6. a. att.). Izmantojot Co(III) kompleksu **7a** kā modeļsubstrātu jauno transformāciju meklēšanai, tika izmēģināti dažādi reaģenti, kas potenciāli varētu piedalīties C-H saites funkcionalizēšanas reakcijās. Veiksmīga C-H saites funkcionalizēšana tika novērota, Co(III) kompleksam **7a** reaģējot ar NFSI. Paaugstinātā temperatūrā (60 °C) tas veicināja C-N saites reducējošo eliminēšanu, veidojot indolu **8**. Pēc produkta struktūras pierādīšanas tika veikta reakcijas apstākļu optimizēšana (6. b. att.). Sākumā tika novērota produkta veidošanās ar 46 % iznākumu, taču pēc vairāku eksperimentu sērijas produkta iznākumu izdevās uzlabot līdz 92 %, kā aktīvā katalizatora prekursoru izmantojot $CoCl_2$ un dpmH ligandu, kā arī aizstājot THF šķīdinātāju ar rūpniecības piemērotāku 2-MeTHF.



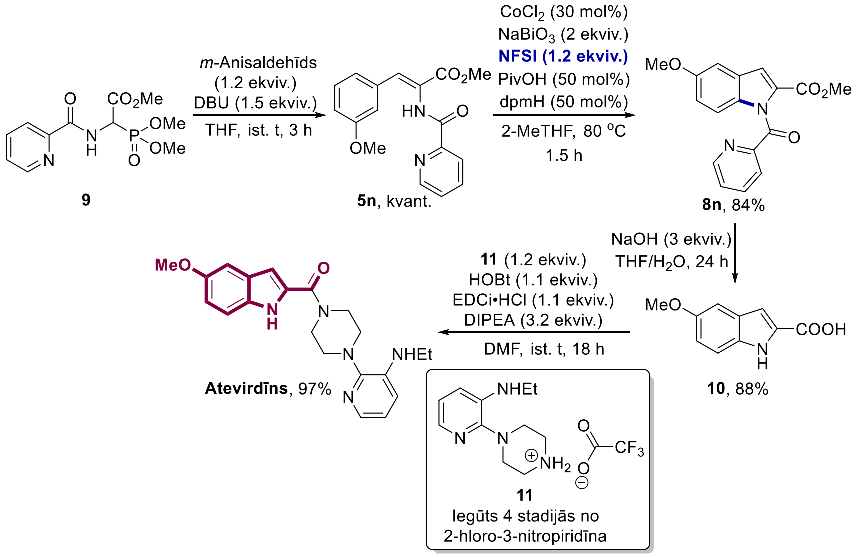
6. att. Kompleksa **7a** reaģētspējas izpēte un reakcijas apstākļu optimizēšana.

Tālāk tika pārbaudīta dažādu funkcionālo grupu savietojamība ar optimizētajiem reakcijas apstākļiem (7. att.). Tika noskaidrots, ka elektrondonoras grupas benzola gredzenā kā alkilgrupa, metoksigrupa un fenilgrupa dažādās pozīcijās dod attiecīgos produktus ar ļoti labiem līdz teicamiem iznākumiem (produkti **8b**, **8c**, **8h**, **8k**, **8l**, **8n**, **8o**, **8q**). Halogēnaizvietoti produkti *orto*- vai *para*- pozīcijās kopumā veidojās ar labiem iznākumiem – no 50 % līdz 84 % (produkti **8d**-**8g**, **8m**, **8r**). Interesanti, ka substrāti, kas saturēja elektronakceptorus aizvietotājus, proti, 4-NO_2 un 4-CN, attiecīgos produktus neveidoja. 2-Naftilaizvietots substrāts **5s** deva produktu **8s** ar 76 % iznākumu kā vienu reģioizomēru. Turklāt *meta*-aizvietoti substrāti (**5n**, **5p**, **5u**) veidoja attiecīgos produktus ar labiem iznākumiem (76 %, 95 %, 71 %), aktivējoties tikai telpiski pieejamākajai C-H saitei.



7. att. Substrātu klāsta izpēte.

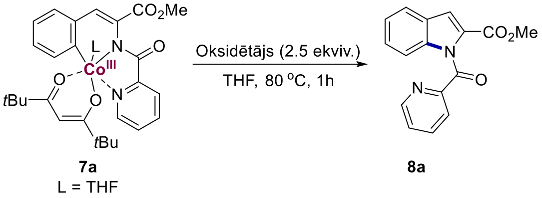
Lai parādītu izstrādātās metodoloģijas izmantošanas iespējas, tika nolemts veikt zāļvielas atevirdīna sintēzi, izmantojot jaunatklāto reakciju kā atslēgstadiju (8. att.). Atevirdīns ir zināms kā apgrieztās transkriptāzes inhibitors, kas tika pētīts *HIV* un *AIDS* ārstēšanai.[17] Tas tika sintezēts, sākot no *m*-anisaldehīda četrās stadijās.



8. att. Atevirdīna sintēzes shēma.

Sākumā *Horner-Wadsworth-Emmons* olefinēšanas reakcijas rezultātā tika iegūts α-amīdoakrilāts **5n**, kas tika izmantots kā substrāts iekšmolekulārai amidēšanai ar NFSI kobalta katalīzes apstākļos, iegūstot attiecīgo produktu **8n** ar ļoti labu iznākumu (84 %). Secīgi, izmantojot nātrija hidroksīdu, vienlaikus tika nošķelta pikolīnamīda virzošā grupa un hidrolizēta estera funkcionālā grupa, iegūstot 5-metoksi indola karbonskābi **10** ar teicamu iznākumu (88 %). Sekojoši, amīdsaites veidošanas reakcijas rezultātā ar amonija sāli **11**, kas tika iegūts četru stadiju sintēzē no komerciāli pieejamā 2-hlor-3-nitropiridīna, tika iegūts Atevirdīns ar izcilu iznākumu.

Lai izprastu reakcijas mehānismu, tika veikti papildu eksperimenti, paredzot, ka reakcija varētu notikt caur Co(IV) intermediātu. Lai to pierādītu, tika veikta indola **8a** sintēze, sākot no Co(III) kompleksa **7a** ar dažādiem organiskajiem un neorganiskajiem oksidētājiem (9. att., 1. tab.).



9. att. Indola **8a** sintēze no kompleksa **7a** ar dažādiem oksidētājiem.

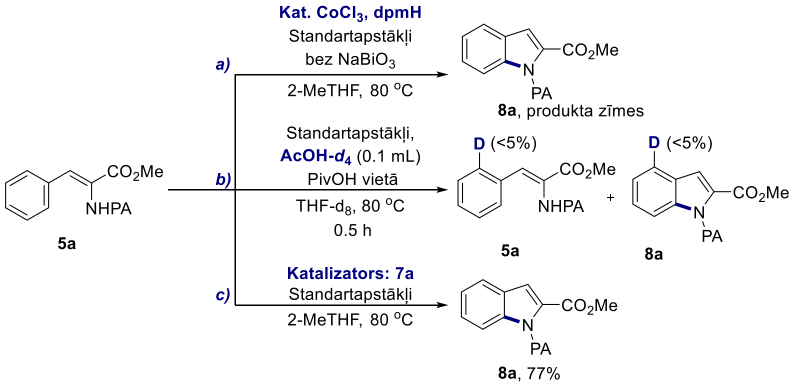
1. tabula

Indola **8a** iznākumi ar dažādiem oksidētājiem

Nr.	Oksidētājs	KMR iznākums, %
1	$PhI(OAc)_2$	33
2	$PhI(OCOCF_3)_2$	79
3	IBX	–
4	CAN	90
5	Ag_2CO_3	–
6	$NaBiO_3$ (2 ekviv.) + NFSI (1.2 ekviv.)	52
7	$NaBiO_3$	–
8	NFSI	76
9	$Mn(OAc)_3 \cdot 2H_2O$	15
10	Bez oksidētāja	–
11	Benzohinons	–

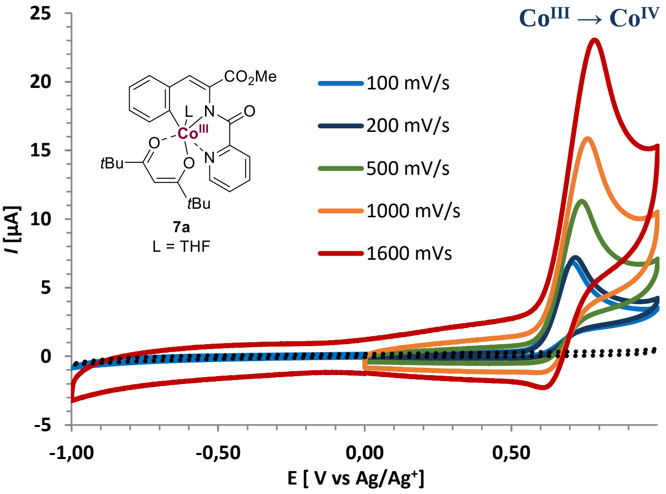
No iegūtajiem datiem tika secināts, ka indola veidošanās notiek tikai spēcīgu oksidētāju klātbūtnē. Šādi rezultāti ļāva izvirzīt hipotēzi, ka reakcijas maisījumā no Co(III) kompleksa **7a** veidojas Co(IV) intermediāts, kas tālāk reducējošās eliminēšanas rezultātā veido indolu, jo no augstākas oksidēšanās pakāpes reducējošā eliminēšana ir atvieglota.

Tālāk tika veikta iekšmolekulāro amidēšanas reakcija standartapstākļos bez $NaBiO_3$ un, aizvietojot $Co(dpm)_2$ katalizatoru ar $Co(dpm)_3$ (10. a. att.), tika novērots, ka substrāts **5a** reakcijā nepiedalās. Šis rezultāts liecināja, ka pirmais solis katalītiskajā ciklā ir Co(II) koordinēšana pie substrāta **5a**, nevis Co(II/III) oksidēšana. Tad tika veikti H/D apmaiņas eksperimenti (10. b. att.). Izmantojot THF-d$_8$ kā šķīdinātāju un deiterētu etiķskābi pivaloilskābes vietā pie nepilnas konversijas, tika novērota < 5 % H/D apmaiņa gan substrāta, gan produkta *orto*-pozīcijā, kas nozīmē, ka C-H saites aktivēšana ir neatgriezeniska. Papildus, lai pārliecinātos, ka komplekss **7a** ir reakcijas intermediāts, tika veikts eksperiments, kā reakcijas katalizatoru izmantojot kompleksu **7a** (10. c. att.). Šajos reakcijas apstākļos tika novērota indola **8a** veidošanās ar 77 % iznākumu.



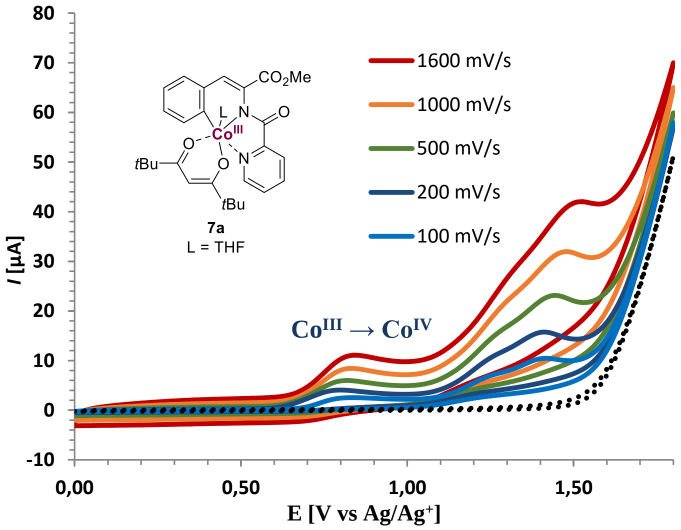
10. att. Mehānisma kontroleksperimenti.

Visām reakcijas komponentēm tika uzņemtas cikliskās voltamogrammas, lai noskaidrotu oksidēšanas potenciālu un iespēju kobaltam oksidēties uz Co(IV). Cikliskā voltamogramma Co(III) kompleksam **7a** 0 °C temperatūrā spriegumā līdz 1 V redzama 11. attēlā. Spriegumā zem 0 V kompleksa reducēšana uz Co(II) nenotiek, kas skaidro šī kompleksa stabilitāti. Savukārt var novērot kvaziapgriezenisku oksidēšanās pīķi pie $E_{\mathrm{max}}^{\mathrm{ox}} = 0{,}84\,V$,[18] kas, visticamāk, ir Co(III/IV) oksidēšanās.



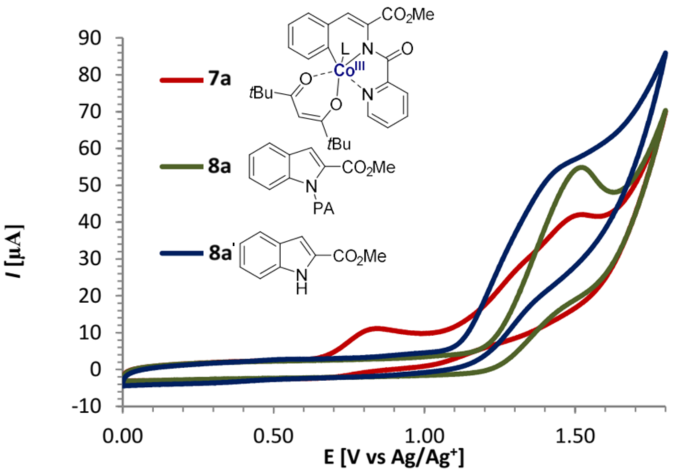
11. att. Cikliskā voltamogramma Co(III) kompleksam **7a** 0 °C temperatūrā līdz 1 V.

Interesanti, ka istabas temperatūrā reakcija nav apgriezeniska un reducēšanas pīķis Co(IV/III) netika novērots (12. att.). To var skaidrot ar Co(IV) intermediāta augsto reaģētspēju. Turklāt, pievadot augstāku spriegumu, tika novēroti papildu pīķi pie $E_{\rm max}^{\rm ox} = 1{,}52\ V$, un pie $E_{\rm max}^{\rm ox} = 1{,}35\ V$.



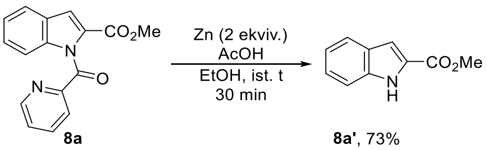
12. att. Cikliskā voltamogramma Co(III) kompleksam **7a** istabas temperatūrā līdz 1,8 V.

Novērotais neapgriezeniskums norādīja, ka kobalta cikls **7a** tiek pārveidots par produktu **8a** oksidēšanas rezultātā, kas nozīmē, ka teorētiski šo pārvērtību ir iespējams panākt elektroķīmiskajos apstākļos.[19] Tika pierādīta indola **8a** veidošanās CV apstākļos, salīdzinot cikliskās voltamogrammas kompleksam **7a** un indola produktam **8a** (13. att.).



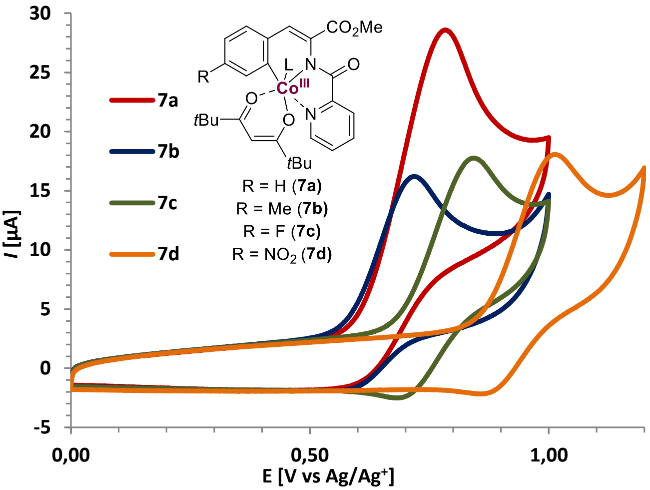
13. att. Cikliskā voltamogramma Co(III) kompleksam **7a**, indola produktam **8a** un indolam ar nošķeltu pikolīnamīda virzošo grupu istabas temperatūrā.

Diemžēl pēdējais redoks pīķis joprojām nebija identificēts. Tika izvirzīta hipotēze, ka pikolīnamīda virzošā grupa varētu tikt nošķelta CV eksperimentu apstākļos. Šim nolūkam, izmantojot cinka un etiķskābes maisījumu etanolā, tika panākta pikolīnamīda virzošās grupas selektīva nošķelšana, iegūstot indola-2-karboksilātu **8a'** ar labu iznākumu – 73 % (14. att.). Uzņemot CV indola atvasinājumam **8a'**, tika noskaidrots, ka savienojuma CV pilnībā sakrīt ar nezināmo redoks pīķi.



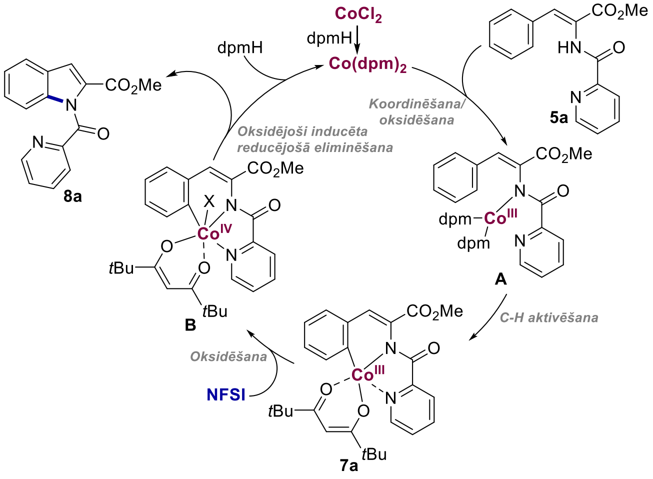
14. att. Selektīva pikolīnamīda nošķelšana.

Lai noteiktu korelāciju starp kobalta kompleksu aizvietotāju īpašībām, tika veikti CV eksperimenti Co(III) kompleksiem **7a-7d** ar dažādiem aizvietotājiem (15. att.). Iegūtie rezultāti attēlo paaugstinātu oksidēšanas potenciālu elektronakceptoru grupu gadījumos, kas skaidro zemāku reaģētspēju substrātiem, kas satur līdzīgus aizvietotājus.



15. att. Co(III) kompleksu **7a**-**7d** voltamogrammas.

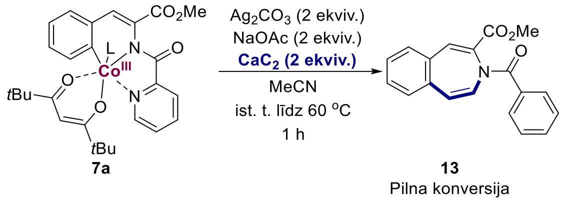
Balstoties promocijas darba autora grupas pētījumos un literatūras precedentos, tika piedāvāts iespējamais reakcijas mehānisms, kas redzams 16. attēlā. Sākumā veidojas aktīvais katalizators Co(dpm)$_2$ no CoCl$_2$ un dpmH liganda. Tad Co(II) katalizators koordinējas pie substrāta **5a** un tiek oksidēts līdz Co(III) ar NaBiO$_3$, veidojot intermediātu **A**, kas C-H saites aktivēšanas rezultātā veido kobalta kompleksu **7a**. Komplekss **7a** tālāk tiek oksidēts līdz Co(IV) intermediātam **B** ar NFSI, kas reducējošās eliminēšanas rezultātā veido galaproduktu **8a**. Alternatīvi pārvērtību no **7a** uz **8a** var saukt par oksidējoši inducētu reducējošo eliminēšanu. Noslēgumā ligandu apmaiņas rezultātā Co(II) tiek atgriezts katalītiskajā ciklā.



16. att. Iespējamais reakcijas mehānisms.

2. Kobalta katalizēta 3-benzazepīnu sintēze

Turpinot darbu pie kompleksa **7a** reaģētspējas izpētes, tika atklāts, ka kobalta kompleksa **7a** reakcijas rezultātā ar kalcija karbīdu veidojās benzazepīns **13** (17. att.).[20, 21] Svarīgi pieminēt, ka, sākot reakciju no kobalta cikla **7a**, tika novērota pilna izejvielas konversija un veidojās tikai viens produkts – savienojums **13**.

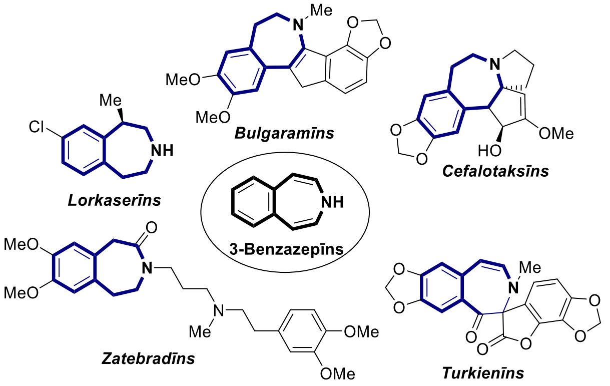


17. att. Benzazepīna **13** iegūšana no Co(III) kompleksa **7a**.

Kalcija karbīdu jeb kalcija acetilīdu rūpniecībā lielā mērogā izmanto acetilēna iegūšanai. Acetilēna sintēze notiek atbilstoši reakcijas vienādojumam:

$$CaC_2 + 2H_2O \rightarrow C_2H_2 + Ca(OH)_2$$

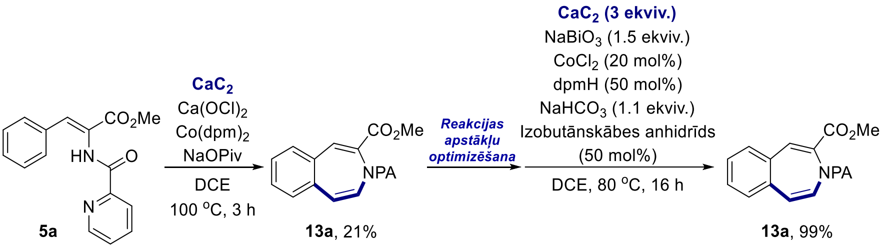
Neskatoties uz to, ka literatūrā ir daudz zināmu metožu, kur kalcija karbīdu izmanto pārejas metālu katalizētās reakcijās, nav neviena piemēra, kur CaC_2 tiktu izmantots tiešā C-H saites aktivēšanas un funkcionalizēšanas reakcijā kā acetilēna gāzes avots. Turklāt 3-benzazepīni ir bieži sastopami fragmenti dažādās zāļvielās, dabasvielās un alkaloīdos (18. att.), piemēram, alkaloīdi – cefalotoksīns,[22] bulgaramīns,[23] turkienīns,[24] pretaptaukošanās medikaments lorkaserīns, kā arī bradikardijas aģents zatebradīns.[25, 26]



18. att. 3-Benzazepīna fragments zāļvielās un dabasvielās.

Tā kā tieša C-H saites aktivēšana un funkcionalizēšana, kā acetilēna avotu izmantojot CaC_2, līdz šim nebija zināma, tika nolemts izpētīt un attīstīt šo pārvērtību kobalta katalīzes apstākļos.

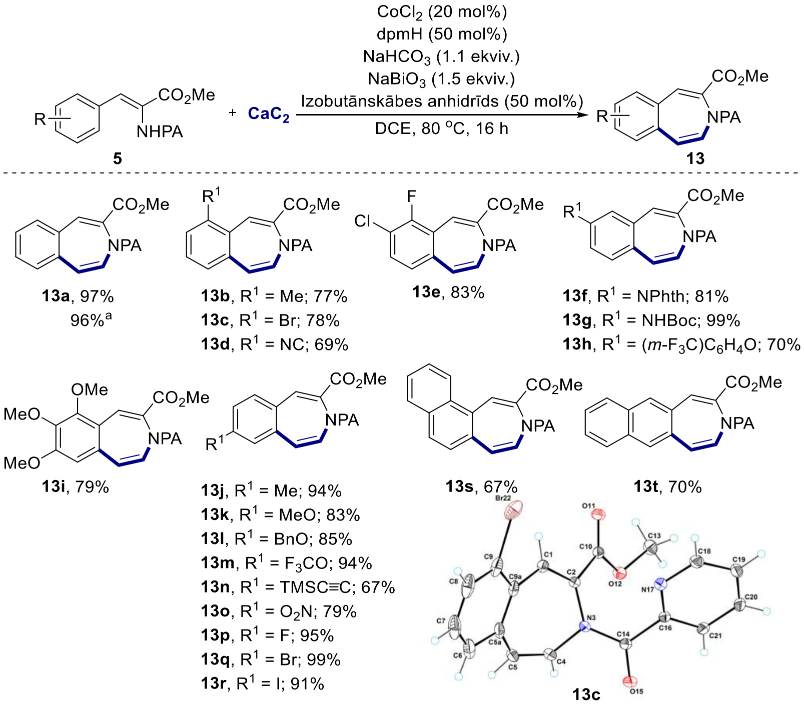
Reakcijas apstākļu optimizēšanai par modeļsubstrātu tika izvēlēts amīdoakrilāts **5a** (19. att.). Optimizējot reakcijas apstākļus, tika izpētīts plašs Co(II) katalizatoru un oksidētāju klāsts, dažādas bāzes/skābes piedevas, kā arī šķīdinātāji un reakcijas temperatūra. Pētījuma sākumā tika novērota produkta veidošanās ar 21 % iznākumu, kā oksidētāju izmantojot kalcija hipohlorītu, taču pēc vairāku eksperimentu sērijas produkta **13a** KMR iznākumu izdevās paaugstināt līdz 99 %, izmantojot $CoCl_2$/dpmH kā aktīvo katalizatora sistēmu, $NaBiO_3$ kā oksidētāju, $NaHCO_3$ kā piedevu un izobutānskābes anhidrīdu kā ligandu. Literatūrā ir zināmas dažas C-H funkcionalizēšanas reakcijas, kurās anhidrīda pievienošana būtiski uzlaboja produkta iznākumu. Tas varētu būt saistīts ar to, ka anhidrīds kalpo kā ligands metāla katalizatoram noteiktā katalītiskā cikla posmā, tādējādi uzlabojot reakcijas ātrumu.[27]



19. att. Reakcijas apstākļu optimizēšana.

Pēc reakcijas apstākļu optimizēšanas promocijas darba autors un viņa kolēģi pievērsās substrātu klāsta izpētei (20. att.), un viņiem izdevās izolēt benzazepīnu **13a** ar 97 % iznākumu optimizētajos reakcijas apstākļos. Veicot reakciju ar palielinātu izejvielas iekrāvumu (1 grams), produkta iznākums praktiski nesamazinājās, un benzazepīns **13a** tika iegūts ar 96 % iznākumu. Tālāk tika pārbaudīta aizvietotāju ietekme uz substrātu reaģētspēju un reakcijas reģioselektivitāti. Izejvielas **5** ar aizvietotājiem *orto*-, *meta*- un *para*-pozīcijās deva attiecīgus produktus **13** ar labiem līdz kvantitatīviem iznākumiem. Izmantojot *meta*-aizvietotus substrātus **5f**–**h**, tika novērota augsta reakcijas reģioselektivitāte un tika iegūti benzazepīni **13f**–**h**, aktivējoties tikai tai C-H saitei, kas ir stēriski mazāk apgrūtināta. Reakcijas apstākļos tika novērota augsta funkcionālo grupu savietojamība, piemēram, tādas elektronus dodošas grupas benzola gredzenā kā metil-(produkti **13b**, **13j**) un metoksi- (**13i**, **13k**), kā arī salīdzinoši stipras elektronus atvelkošas grupas kā ciāno- (**13d**), un nitro-grupa (**13o**) deva attiecīgos produktus ar labiem iznākumiem. Papildus tam, halogēnus saturošie substrāti **5** optimizētajos reakcijas apstākļos deva attiecīgos produktus ar iznākumiem no 78 % līdz pat 99 % (produkti **13c**, **13e**, **13p**–**r**).

Kristālizējot produktu **13c** no THF, izdevās iegūt monokristālus un pierādīt produkta **13c** struktūru ar rentgenstruktūranalīzes palīdzību. Arī stēriski apgrūtināti substrāti **5e** un **5i** deva attiecīgos produktus **13e** un **13i** ar ļoti labiem iznākumiem (83 % un 79 %), tāpat arī substrāti ar aizsargātām aminogrupām bija piemēroti annulēšanas reakcijai, dodot produktus **13f** un **13g** ar teicamiem iznākumiem. Tika atklāts arī tas, ka abi divi – naftalīn-1-il un naftalīn-2-il amīdoakrilāti – **5s** un **5t** ļoti labi reaģēja optimizētajos reakcijas apstākļos, kā rezultātā tika iegūti naftilazepīni **13s** un **13t** ar 67 % un 70 % iznākumiem.

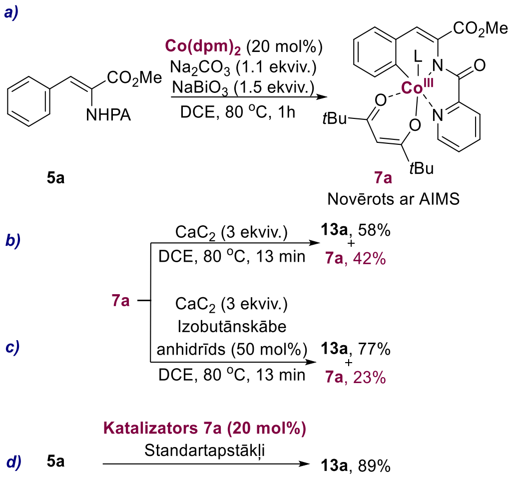


^{a}Substrāta iekrāvums: 1 grams

CCDC 2390205

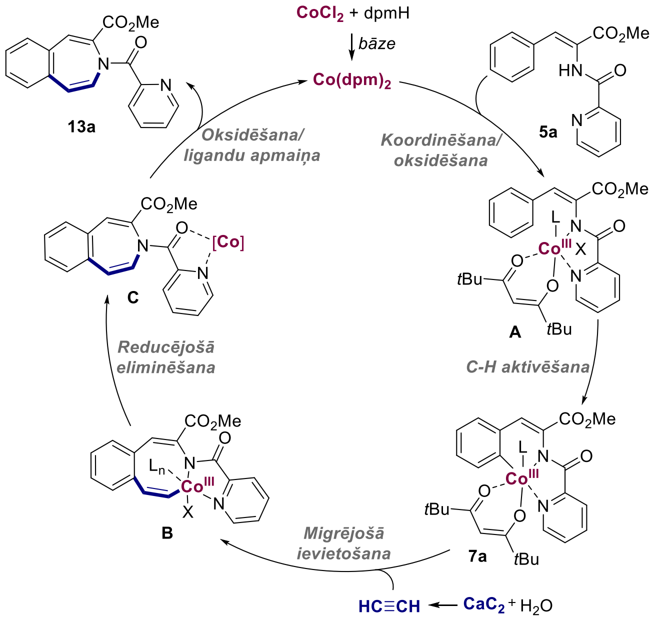
20. att. Substrātu klāsta izpēte.

Lai izprastu reakcijas mehānismu, tika veikti papildu eksperimenti. Sākumā reakcijas maisījumā ar augstas izšķirtspējas masas analīzi (AIMS) tika detektēts kobalta komplekss **7a** (21. a. att.). Tika sintezēts Co(III) komplekss **7a**, izmantojot iepriekš izstrādātu metodi, un tika pierādīts, ka tas ir reakcijas intermediāts. Stehiometriskie eksperimenti, izmantojot Co(III) kompleksu **7a** kā substrātu, tika analizēti pie nepilnas konversijas bez (21. b. att.) vai izobutānskābes anhidrīda klātbūtnē (21. c. att.). Iegūtie rezultāti liecināja, ka anhidrīda klātbūtnē reakcija notiek nedaudz ātrāk. No šī eksperimenta tika secināts, ka izobutānskābes anhidrīds visdrīzāk kalpo kā ligands pēc C-H saites aktivēšanas soļa, paātrinot reducējošo eliminēšanu vai acetilēna migrējošo ievietošanos. Izmantojot kobalta kompleksu **7a** kā katalizatoru (21. d. att.), tika iegūts benzazepīns **13a** ar 89 % iznākumu, kas tika noteikts ar KMR spektroskopiju.



21. att. Kontroles eksperimenti.

Balstoties mehānisma pētījumos un literatūras precedentos, iespējamais reakcijas mehānisms parādīts 22. attēlā.

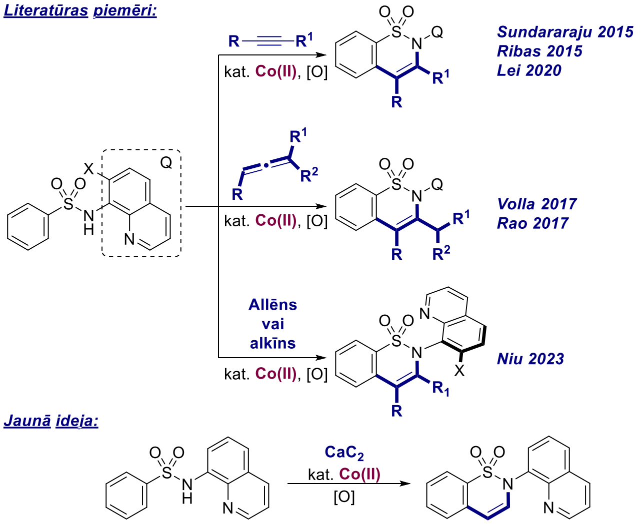


22. att. Iespējamais 3-benzazepīna **13a** veidošanās mehānisms.

Sākumā veidojas aktīvais katalizators Co(dpm)$_2$ no CoCl$_2$ un dpmH liganda bāzes klātienē. Co(II) katalizators koordinējas pie substrāta, un pēc oksidēšanas/C-H aktivēšanas sekvences veidojas kobalta cikls **B**. Iespējams, kobalta komplekss **B** apmaina ligandus no dpm uz izobutānskābes anhidrīdu pirms alkīna migrējošās ievietošanas. Tad acetilēna koordinēšana un migrējošā ievietošanās veido kobalta kompleksu **C**, kas pēc reducējošās eliminēšanas veido **D**. Pēc demetalēšanas kobalta intermediāts **D** veido produktu **13a**, un kobalts tiek reoksidēts, lai atsāktu katalītisko ciklu.

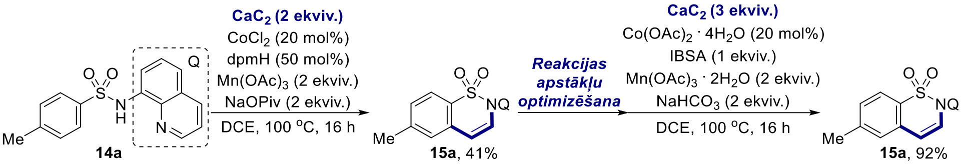
3. Kobalta katalizēta sulfonamīdu un benzamīdu C-H saites annulēšana

Tālākā pētījumu gaitā tika pārbaudīts, vai C-H saites annulēšanas metodoloģiju ar kalcija karbīdu varētu lietot arī benzosulfonamīdu atvasinājumiem. Kopš 2015. gada literatūrā ir publicētas vairākas metodes sulfonamīdu annulēšanai, kā reaģentus izmantojot aizvietotus alkīnus vai allēnus,[28–32] kā arī ir izstrādāta metode atroposelektīvai annulēšanas reakcijai (23. att.).[33] Neskatoties uz ievērojamu progresu sulfonamīdu C-H saites annulēšanas jomā pēdējo desmit gadu laikā, metodoloģijā nav zināmu piemēru C3/C4 neaizvietotu benzosultāmu iegūšanai. Tika paredzēts, ka sulfonamīdi ar kalcija karbīdu reaģēs līdzīgi kā ar α-amīdoakrilātu atvasinājumiem, dodot neaizvietotus benzosultāmus kobalta katalīzes apstākļos.



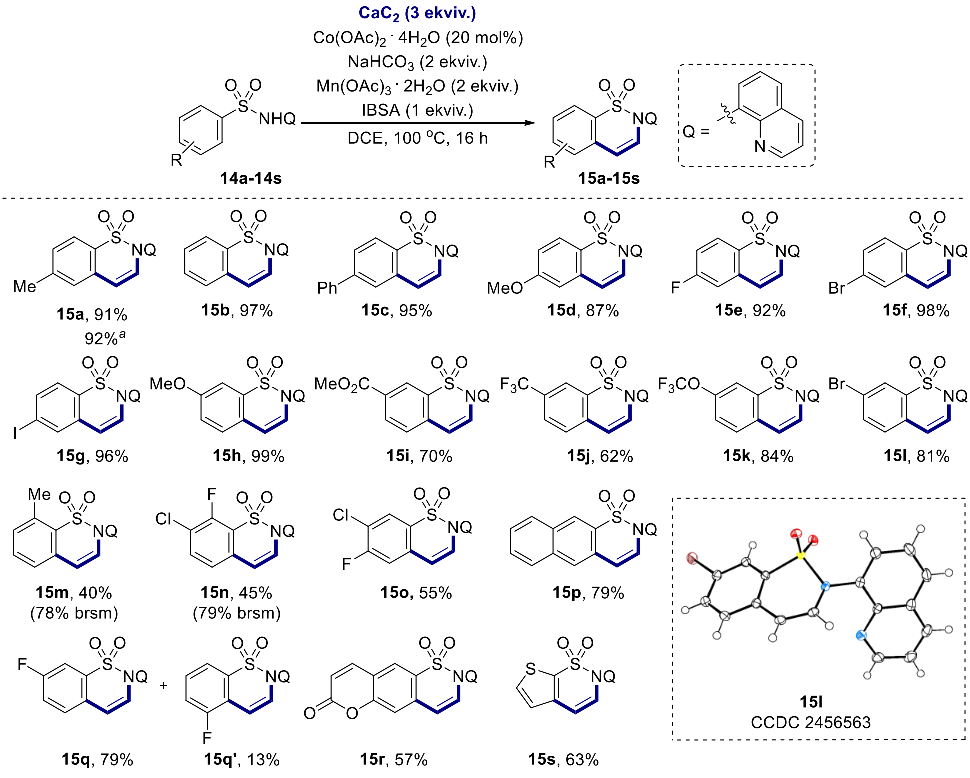
23. att. Kobalta-katalizēta C-H saites annulēšana.

Reakcijas optimizēšanas pētījumos par substrātu tika izmantots *p*-toluolilsulfonamīds **14a**, kas saturēja 8-aminohinolīna virzošo grupu (24. att.). Eksperimentos tika noskaidrots, ka veiksmīgai reakcijas norisei ir nepieciešams izmantot šādu katalītisku sistēmu: $Co(OAc)_2 \cdot 4H_2O$ kā katalizatoru, $NaHCO_3$ kā piedevu, $Mn(OAc)_3 \cdot 4H_2O$ kā oksidētāju, un izobutānskābes anhidrīdu kā ligandu.



24. att. Sulfonamīdu **14a** annulēšanas reakcijas apstākļu optimizēšana.

Tālāk tika pārbaudīta dažādu funkcionālo grupu savietojamība ar optimizētajiem reakcijas apstākļiem (25. att.). Tika novērots, ka sulfonamīdi **14a-14s** ar *orto-*, *meta-* un *para-*aizvietotājiem izturēja reakcijas apstākļus, ļaujot iegūt attiecīgos produktus ar kopumā labiem līdz teicamiem iznākumiem (40–99 %).



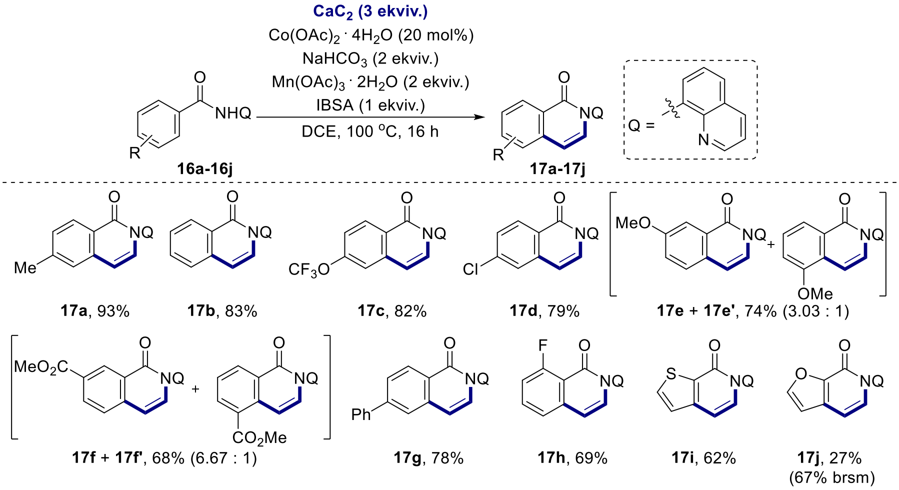
aSubstrāta iekrāvums: 1 grams

25. att. Kobalta katalizēta benzosultāmu **15** sintēze.

Tādas elektrondonoras grupas kā alkil- (produkti **15a**, **15m**), alkoksi- (**15d**, **15h**), fenil- (**15c**), elektronakceptoras grupas kā trifluormetil- (**15j**), trifluormetoksi- (**15k**) un metil esteris (**15i**) benzola gredzenā ļāva iegūt vēlamos annulēšanas produktus. Metilgrupu saturošs substrāts **14a** un neaizvietots substrāts **14b** deva attiecīgos produktus ar teicamiem iznākumiem – 91 % un 97 %. Turklāt, palielinot izejvielas **14a** iekrāvumu līdz 1 g, produkta iznākums būtiski nemainījās. Halogēnus saturošie savienojumi **14e**, **14f**, **14g**, **14l**, **14n** un **14o** deva attiecīgos benzosultāmus ar vidējiem un ļoti labiem iznākumiem (līdz 98 %). Ir vērts pieminēt, ka *meta*-aizvietotas izejvielas deva attiecīgos produktus **15h**-**15l** ar labiem iznākumiem (62–99 %) kā vienu reģioizomēru. Kristalizējot produktu **15l** no THF, izdevās iegūt monokristālus un pierādīt savienojuma struktūru ar rentgenstruktūranalīzes palīdzību. Interesanti, ka 3-fluorbenzosulfonamīds **14q** bija piemērots substrāts annulēšanas reakcijā, taču šajā gadījumā reakcija nebija selektīva un tika izolēti abi reģioizomēri **15q** (79 %) un **15q'** (13 %).[34] Stēriski apgrūtināti *orto*-aizvietotas izejvielas **14m** un **14n** deva attiecīgos produktus **15m** un **15n** ar viduvējiem iznākumiem – 40 % un 45 % attiecīgi, turklāt zemie iznākumi ir saistīti ar vāju substrātu reaģētspēju. Naftalēn-2-ilsulfonamīds **14p** arī demonstrēja labu reaģētspēju, ļaujot iegūt naftosultāmu **15p** ar 79 % iznākumu kā vienu reģioizomēru. Papildus tam heterocikliski sulfonamīdi **14r** un **14s** bija piemēroti atklātajiem reakcijas apstākļiem un deva produktus **15r** un **15s** ar labiem iznākumiem.

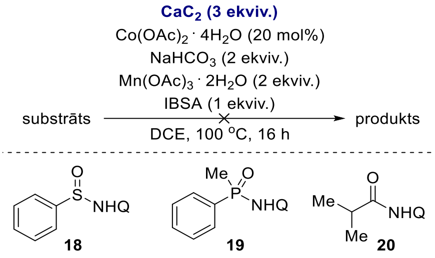
Iedvesmojoties no iegūtajiem rezultātiem sulfonamīdu **14** annulēšanas reakcijās ar kalcija karbīdu, tika nolemts lietot šo metodi arī benzamīda substrātiem **16** (26. att.). Promocijas darba autors un viņa kolēģi bija patīkami pārsteigti, ka produkta veidošanās notika standartapstākļos un papildu reakcijas apstākļu modificēšana nebija nepieciešama.

Tika novērots, ka dažādas funkcionālas grupas bija savietojamas ar reakcijas apstākļiem. Benzamīdi **16** ar elektronus dodošām grupām (produkti **17a**, **17g**), elektronus atvelkošām grupām (produkts **17c**), kā arī neitrāli un halogēnus saturoši benzamīdi (produkti **17b**, **17d**) piedalījās annulēšanas reakcijā un deva vēlamus produktus ar ļoti labiem līdz teicamiem iznākumiem (78–93 %). Diemžēl optimizētajos reakcijas apstākļos *meta*-aizvietoti benzamīdi ar metoksi- un metilestera funkcionālajām grupām veidoja produktus kā neatdalāmus reģioizomēru maisījumus. Neskatoties uz to, reģioizomēru attiecība bija pieņemama, kā arī produktu **17e** un **17f** iznākumi bija attiecīgi 74 % un 68 %. Pretēji benzosultāmiem *orto*-aizvietots produkts **17h** veidojās ar labu iznākumu – 69 %. Turklāt divi heterocikliskie amīdi tika pakļauti C-H saites funkcionalizēšanai ar kalcija karbīdu. Rezultātā tiēnpiridinons **17i** tika iegūts ar 62 % iznākumu, savukārt furānpiridinons **17j** tika izolēts ar 27 % iznākumu. Šajā gadījumā zemais produkta iznākums tika attiecināts uz izejvielas zemo reaģētspēju piedāvātājos apstākļos.



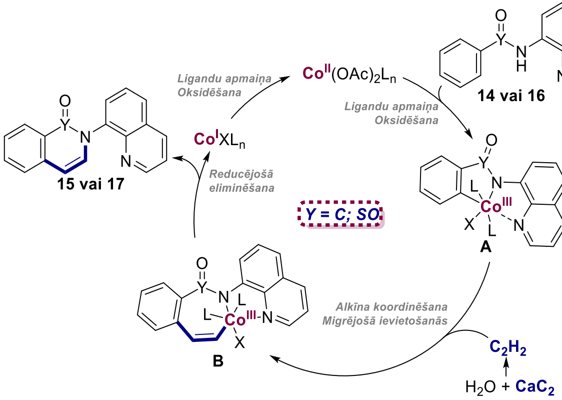
26. att. Kobalta katalizēta benzamīdu **16** C-H saites annulēšana ar CaC_2.

Pētot izstrādātās metodes substrātu klāstu, tika atklāti vairāki metodes ierobežojumi (27. att.). Tādi substrāti kā sulfīnamīds **18** vai fosfīnamīds **19** nebija stabili reakcijas apstākļos, un rezultātā tika konstatēts neidentificēts blakusproduktu maisījums un tikai vēlamā produkta zīmes. Tajā pašā laikā izobutiramīds **20** reakcijas apstākļos nereaģēja, ko var skaidrot ar to, ka $C(sp^3)$-H saites aktivēšanai un funkcionalizēšanai ir nepieciešami skarbāki reakcijas apstākļi, pateicoties lielai C-H saites disociācijas enerģijai.



27. att. Neveiksmīgie substrāti C-H saites annulēšanas reakcijā.

Nesen tika demonstrēts, ka 8-aminohinolīna virzītām kobalta katalizētām C-H saites funkcionalizēšanas reakcijām ir iespējami divi katalītiskie cikli – Co(I)/Co(III) un caur Co(IV).[35] Balstoties promocijas darba autora un viņa kolēģu grupas iepriekšējos pētījumos[11, 14, 15, 36] un literatūras piemēros,[18, 19, 28–32, 37] ir ļoti mazticams, ka Co(IV) intermediāta izveide šajā gadījumā ir iespējama. Balstoties šajos piemēros, tika piedāvāts Co(I)/Co(III) katalītiskais cikls (28. att.).



28. att. Iespējamais sulfonamīdu un benzamīdu C-H saites annulēšanas mehānisms.

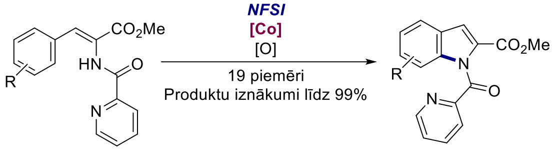
Sākumā Co(II) katalizators koordinējas pie sulfonamīda **14** vai benzamīda **16**, un tad sekojošās oksidēšanas un C-H saites aktivēšanas rezultātā veido kobalta kompleksu **A**. Acetilēna gāzes migrējošās ievietošanās rezultātā veidojas vinil- kobalta komplekss **B**, kas reducējošās eliminēšanas ceļā veido sultāmu **15** vai izohinolīnonu **17** kopā ar Co(I), kas pēc reoksidēšanas un ligandu apmaiņas atjauno katalītisko ciklu.

Promocijas darba izstrādes gaitā tika atklāta jauna kobalta katalizēta iekšmolekulāra amidēšana. Kā substrātus izmantojot α-amīdoakrilātu atvasinājumus **5**, bija iespējams iegūt indolu produktus **8** ar dažādiem azivietotājiem benzola gredzenā, kā arī reakcija tika lietota zāļvielas Atevirdīna sintēzē. Veicot intermediātu sintēzi, kontroleksperimentus un cikliskās voltametrijas eksperimentus, tika pierādīta Co(IV) intermediāta veidošanās reakcijā un piedāvāts iespējamais reakcijas mehānisms.

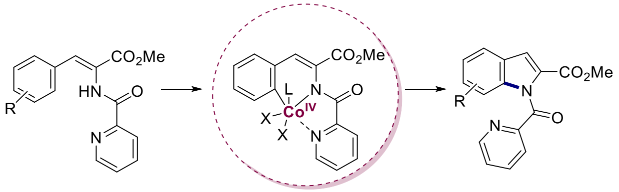
Turklāt tika izstrādātas divas metodes kobalta katalizētai C-H saites annulēšanai, kā izejvielas izmantojot α-amīdoakrilātu **5**, sulfonamīdu **14** un benzamīdu **16** atvasinājumus. Jaunizstrādātās metodēs kā acetilēna gāzes avots tika izmantots kalcija karbīdu. Pētījumu gaitā tika veikta rūpīga un daudzpusīga substrātu klāstu izpēte, kā arī tika piedāvāti reakcijas mehānismi, balstoties literatūrā zināmās pārvērtībās un promocijas darba autora un viņa kolēģu mehānisma kontroleksperimentos.

SECINĀJUMI

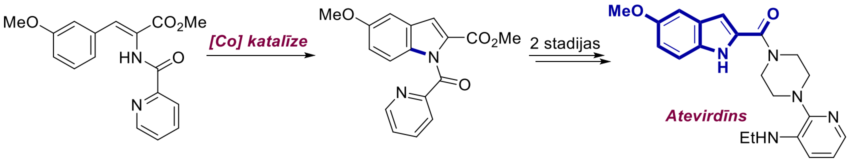
1. Kobalta katalīzes apstākļos, kā virzošo grupu izmantojot pikolīnamīdu, ir iespējams panākt α-amīdoakrilātu atvasinājumu iekšmolekulāru ciklizēšanu par indola atvasinājumiem.



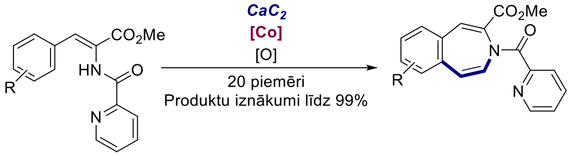
2. Balstoties kontroleksperimentos, cikliskās voltametrijas datos un datoraprēķinos, tika pierādīts, ka α-amīdoakrilātu iekšmolekulārā amidēšana notiek caur oksidējoši inducētu reducējošo eliminēšanu, ietverot Co(IV) intermediātu.



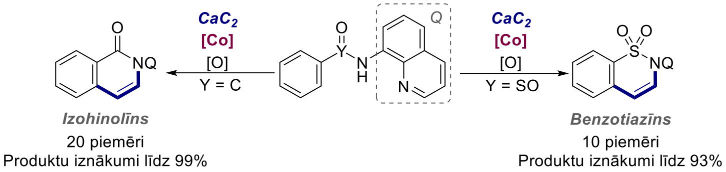
3. Izstrādāto metodi indola cikla saslēgšanai var izmantot zāļvielas Atevirdīna, kā arī tās potenciālo analogu sintēzē, sākot no komerciāli pieejamiem dažādi aizvietotiem aldehīdiem.



4. Kobalta katalizētā α-amīdoakrilātu C-H saites annulēšanas reakcijā, pateicoties kalcija karbīda spējai ģenerēt *in situ* acetilēna gāzi, ir iespējams iegūt 3-benzazepīna atvasinājumus.



5. Kobalta katalizētā arilsulfonamīdu un benzamīdu C-H saites annulēšanas reakcijā, kā acetilēna gāzes avotu izmantojot kalcija karbīdu, ir iespējams iegūt benzosultāma un izohinolīna atvasinājumus.



DOCTORAL THESIS PROPOSED TO RIGA TECHNICAL UNIVERSITY FOR PROMOTION TO THE SCIENTIFIC DEGREE OF DOCTOR OF SCIENCE

To be granted the scientific degree of Doctor of Science (PhD), the present Doctoral Thesis has been submitted for defence at the open meeting of RTU Promotion Council on 4 December 2025 at 14.00 at the Faculty of Natural Sciences and Technology of Riga Technical University, Paula Valdena iela 3, Room 272.

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DECLARATION OF ACADEMIC INTEGRITY

I hereby declare that the Doctoral Thesis submitted for review to Riga Technical University for promotion to the scientific degree of Doctor of Science (PhD) is my own. I confirm that this Doctoral Thesis has not been submitted to any other university for promotion to a scientific degree.

Aleksandrs Čižikovs ……………………………. (signature)
Date: ………………………

The Doctoral Thesis has been prepared as a thematically united collection of scientific publications. It consists of a Summary, three scientific publications, two review publications and one book chapter. Publications are written in English. The total number of pages is 501, including electronic supporting information.

GENERAL OVERVIEW OF THE THESIS

Introduction

The main aim of organic synthetic chemistry is to design and synthesize more complex structures from simple molecules. Classic organic synthesis often relies on the manipulations of functional groups – a reaction sequence to obtain the desired products. In organic chemistry, the term "C-H bond functionalization" is used to describe a chemical reaction, in which a C-H bond of a substrate is cleaved and replaced with C-C, C-N, C-S, C-Hal or any other bond (Fig. 1). Unfortunately, this type of transformation often cannot be realized due to the low reactivity or insufficient acidity of the C-H bond. To overcome this obstacle, chemists have developed a novel approach to activate and functionalize the C-H bond using transition metal catalysts. Today, transition metal-catalyzed C-H bond activation and functionalization is a significant part of organic synthesis and has an ongoing impact in the fields of new drug discovery, materials science, and the synthesis of various natural products.[1–3]

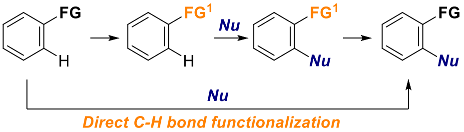


Fig. 1. General scheme for C-H bond functionalization.

Most of the C-H bond activation and functionalization reactions are relatively easily performed using noble metal (e.g., ruthenium, rhodium, iridium, palladium, etc.) catalysts. Moreover, these catalysts have shown high reactivity and selectivity. Despite the reactivity these metals have shown, their use in organic synthesis is not sustainable and might be limited in future due to their low abundance, high toxicity and expense.[4]

Cobalt is a period 4 group 9 element with an atomic number of 27. Additionally, it can be found in vitamin B12 – cyanocobalamine, which makes cobalt an essential metal to living organisms. Moreover, being a cheaper and more attractive alternative to precious metal catalysts, cobalt compounds in various oxidation states are being extensively studied and used as catalysts in organic synthesis.[2]

Cobalt-catalyzed C-H bond activation and functionalization reactions can be divided into two groups: low-valent cobalt catalysis with cobalt in its oxidation states 0 or +1, and high-valent cobalt catalysis, where cobalt has an oxidation state +3, starting from either Co(III) or Co(II) salts under oxidative conditions.[5, 6] Scientific attention towards cobalt-catalyzed reactions dates back to 1941, when Kharasch and Fields published their study, which showed that Grignard reagents can dimerize in the presence of cobalt dichloride.[7] Later, in 1955, a Japanese chemist, Murahashi, first developed a cobalt-catalyzed C-H bond functionalization reaction using low-valent dicobalt octacarbonyl as the reaction catalyst.[8] Since the introduction of cobalt-catalyzed C-H bond functionalization reactions, the most significant advances have been made using low-valent cobalt catalysis. However, starting from around 2013–2014, interest in the use of high-valent Co(III) and its precursor Co(II) started to increase. In the following years, this type of reaction became an important research area. Nowadays, high-valent cobalt catalysis is combined with green chemistry strategies, including replacing metal oxidants with electricity,[9] using cheap reactant precursors to generate toxic gases,[10, 11] combining photo-redox reactions with transition-metal chemistry,[12] using easily cleavable directing groups,[13] etc.

In our groups' previous studies, we developed effective methods for C-H bond functionalization of amino alcohol and amino acid derivatives (Fig. 2). We discovered that differently substituted phenylglycinols **1** can be successfully transformed into isoindolinones **2** under the C-H bond carbonylation conditions, using DIAD as a CO gas surrogate (Fig. 2 a).[10] Afterwards, working with amino acid derivatives, we enclosed C-H bond carbonylation (Fig. 2 b)[14] and imination (Fig. 2 c)[15] reactions of phenylalanine derivatives **3** and **5**, delivering isoquinolinone **4** and iminoisoquinoline **6** derivatives. Interestingly, under carbonylation conditions, the picolinamide directing group was cleaved *in situ*.

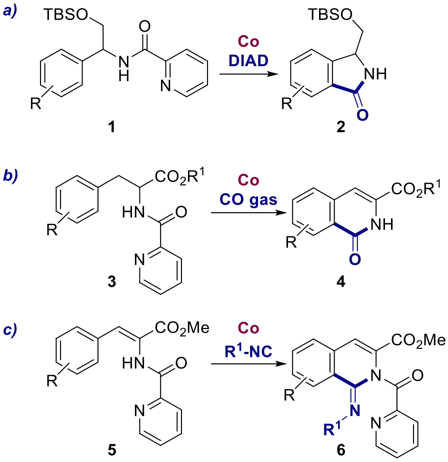


Fig. 2. Previous studies on cobalt-catalyzed synthesis of heterocycles **2**, **4** and **6**.

The development of novel methods for the synthesis of heterocyclic compounds, both new and known, could not only contribute to the development of new synthetic approaches but also potentially reduce the cost of production of existing pharmaceuticals. Therefore, our research is focused on the development of novel cobalt-catalyzed C-H bond activation and functionalization methods for the synthesis of various heterocyclic compounds. The methods developed in the Thesis are based on high-valent cobalt catalysis, using simple Co(II) salts in combination with a bidentate directing group as precursors of Co(III) species (Fig. 3).

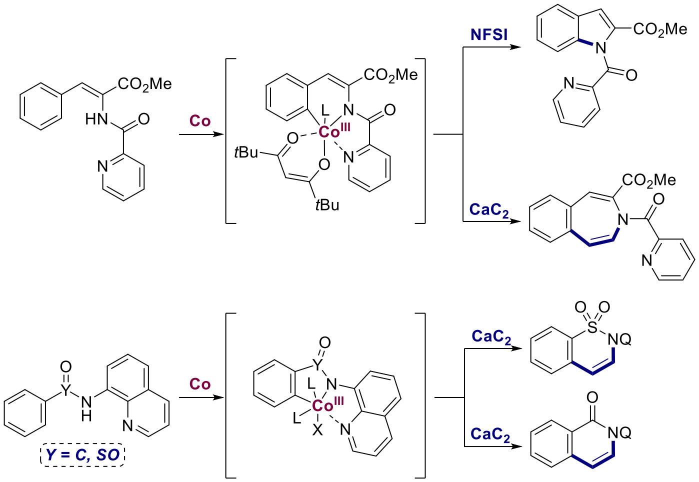


Fig. 3. Possible synthetic approaches for various heterocycles *via* cobalt catalysis.

Aims and objectives

The aim of the Thesis is to develop novel, practical and convenient C-H bond functionalization methods under cobalt catalysis for the synthesis of relevant heterocyclic compounds. To achieve this aim, the following tasks were set:

1. Synthesize α-amidoacrylate, sulfonamide and benzamide derivatives, which could be potentially employed as substrates for C-H bond activation and functionalization reactions.
2. Conduct a literature search and identify appropriate reagents that could participate in cobalt-catalyzed C-H bond functionalization reactions.
3. Optimize the reaction conditions and investigate the substrate scope to determine limitations of the developed methodology. Conduct the necessary experiments to investigate the possible mechanism of the reaction.

Scientific novelty and main results

As result of the Thesis, two novel C-H bond functionalization methods of α-amidoacrylate derivatives and one novel C-H bond annulation method of sulfonamide and benzamide were developed:

1. indole synthesis *via* cobalt-catalyzed C-H bond intramolecular amidation of α-amidoacrylate derivatives;
2. cobalt-catalyzed C-H bond annulation for the synthesis of 3-benzazepines with CaC_2 as the acetylene source;
3. cobalt-catalyzed sulfonamide and benzamide C-H bond annulation with CaC_2.

Structure of the Thesis

The Thesis was prepared as a thematically unified set of scientific publications on the development of cobalt-catalyzed C-H bond functionalization methods. The Thesis includes a method for the synthesis of indoles by intramolecular amidation of α-amidoacrylate derivatives, a method for the synthesis of 3-benzazepines with calcium carbide as the acetylene gas source, and a methodology for the C-H bond annulation of sulfonamide and benzamide derivatives with calcium carbide. In addition, the Thesis also includes reviews on the mechanistic studies.

Publications and approbation of the Thesis

The main results of the Thesis were summarized in three scientific publications, two reviews, and one book chapter. The results of the research were presented at six conferences and scientific events.

Scientific publications

1. **Cizikovs, A.**, Grigorjeva, L. Cobalt-Catalyzed C-H Annulation of Aryl Sulfonamides and Benzamides with CaC_2 as the Acetylene Source. *Org. Lett.* **2025**, *27*(26), 7070–7074. DOI: 10.1021/acs.orglett.5c01981.
2. **Cizikovs, A.**, Lukasevics, L. T., Zagorska, P. A., Grigorjeva, L. Cobalt-Catalyzed C–H Bond Functionalization: a Personal Account. *Synlett* **2025**, *36*(12), 1659–1668. DOI: 10.1055/s-0043-1775473.
3. **Cizikovs, A.**, Zagorska, P. A., Grigorjeva, L. Synthesis of 3-Benzazepines via Cobalt-Catalyzed C–H Bond Functionalization with CaC_2 as the Acetylene Source. *Org. Lett.* **2024**, *26*, 9536. DOI: 10.1021/acs.orglett.4c03551
4. **Cizikovs, A.**, Basens, E. E., Zagorska, P. A., Kinens, A., Grigorjeva, L. Indole Synthesis by Cobalt-Catalyzed Intramolecular Amidation via the Oxidatively Induced Reductive Elimination Pathway. *ACS Catal.* **2024**, *14*, 1690. DOI: 10.1021/acscatal.3c05706
5. **Cizikovs, A.**, Grigorjeva, L. Co(III) Intermediates in Cobalt-Catalyzed, Bidentate Chelation Assisted C(sp^2)-H Functionalizations. *Inorganics* **2023**, *11*, 194. DOI: 10.3390/inorganics11050194

Book chapter

1. **Cizikovs, A.**, Basens, E. E., Zagorska, P. A., Grigorjeva, L. Diastereoselective C-H Functionalizations. *Comprehensive Chirality, 2nd edition (Ed. J. R. Cossy)*. **2024**, 138. DOI: 10.1016/B978-0-32-390644-9.00101-3

Results of the Thesis were presented at the following conferences

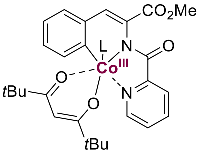
1. **Cizikovs, A.** Development of Novel Methods for the Synthesis of Heterocycles Using Cobalt Catalysis. *Paul Walden 14th Symposium on Organic Chemistry*. Riga, Latvia, 25–26 September **2025**.
2. **Cizikovs, A.,** Grigorjeva, L. Cobalt-Catalyzed C-H Annulation of Aryl Sulfonamides and Benzamides with CaC_2 as the Acetylene Source. *International Symposium on Synthesis and Catalysis 2025*. Coimbra, Portugal, 2–5 September **2025**.
3. Experience exchange visit to the University of Houston to Prof. Olafs Daugulis group. Presentation: "Cobalt-Catalyzed C-H Bond Functionalization" Houston, USA, 12–17 May **2025**.
4. **Cizikovs A.,** Zagorska, P. A., Grigorjeva L. Mechanistic Insights Into Cobalt-Catalyzed C-H Bond Functionalization of α-Amidoacrylates. *7th International Symposium on C-H Activation*. IIT Bombay, Mumbai, India, 6–9 December **2024**.
5. **Cizikovs A.,** Zagorska P. A., Grigorjeva L. CaC_2 – an effective acetylene surrogate for the synthesis of benzoazepine derivatives via cobalt catalysis. *Balticum Organicum Syntheticum 2024 (BOS 2024)*. Riga, Latvia, 7–10 July **2024**.
6. **Cizikovs A.,** Basens E. E., Zagorska P. A., Kinens A., Grigorjeva L. Indole Synthesis by Cobalt-Catalyzed Intramolecular Amidation via the Oxidatively Induced Reductive Elimination Pathway. *European Meeting on C-H Activation*. Lisbon, Portugal, 23–24 January **2024**.
7. **Cizikovs A.,** Basens E. E., Zagorska P. A., Grigorjeva L. Indole synthesis via $C(sp^2)$-H bond functionalization of amino acids. *Paul Walden 13th Symposium on Organic Chemistry*. Riga, Latvia, 14–15 September **2023**.
8. **Cizikovs A.,** Basens E. E., Zagorska P. A., Grigorjeva L. The reactivity of $C(sp^2)$-H activated cobalt complexes: a straightforward synthesis of indoles. *International Symposium on Synthesis and Catalysis 2023*. Évora, Portugal, 5–8 September **2023**.

MAIN RESULTS OF THE THESIS

1. Indole synthesis *via* cobalt-catalyzed α-amidoacrylate intramolecular amidation

To date, various synthetic methods have been developed for the synthesis of indole derivatives, including Fischer indole synthesis and palladium-catalyzed cyclization reactions.[16] Although these methods are often used, they have several limitations, unwanted by-products are formed or the necessity for expensive reagents. For these reasons, the development of new methods for the synthesis of the indole derivatives using 3d group transition metal catalysts (Co, Fe, Mn, etc.) is highly desirable.

In our previous investigations, while studying α-amidoacrylate carbonylation and imination reactions, we were able to isolate C-H activated Co(III) complex **7a** from the reaction mixture. (Fig. 4).[14, 15]



7a

L = CD_3OD

Fig. 4. The structure of isolated C-H activated cobaltacycle **7a**.

We planned to explore the reactivity of isolated cobaltacycles; therefore, we synthesized the complex on a larger scale. Differently substituted Co(III) organic complexes were obtained in one step starting from α-amidoacrylates **5** containing various electronically different substituents, using $Co(dpm)_2$, Ag_2CO_3 and NaOPiv in a small excess (Fig. 5). Crystallization of **7a** from dry THF afforded suitable monocrystals for X-ray analysis, thus the structure of cobalt complex **7a** was unambiguously confirmed.

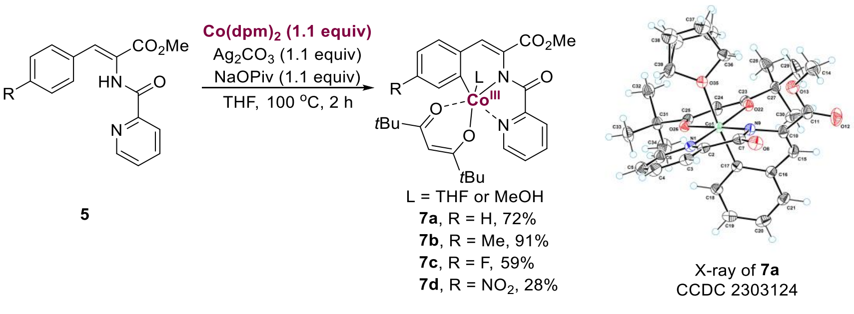


Fig. 5. Synthesis of Co(III) complexes **7a-7d**.

Based on the yields of cobaltacycles **7a-d**, we can conclude that the C-H bond activation of similar substrates depends on electronic effects as electron-rich substrate **5b** (methyl group) gave the corresponding cobalt complex **7b** with a better yield than electron-poor substrate **5d** (nitro group).

Next, we explored the reactivity of complex **7a** (Fig. 6 a). New chemical transformations were discovered employing Co(III) complex **7a** as a model substrate. We tested several reagents that could potentially participate in C-H bond functionalization reactions. Pleasingly, the successful C-H bond functionalization was observed when C-H activated Co(III) complex **7a** reacted with NFSI. At slightly elevated reaction temperature (60 °C), it promoted C-N bond reductive elimination, leading to the formation of indole-2-carboxylate **8**. After the products' structure was fully determined, we switched our attention to the optimization of reaction conditions (Fig. 6 b). First, we observed the formation of the product in 46 % yield, but after reaction optimization, we were able to increase product yield to 92 %, using $CoCl_2$ and dpmH ligand as a precursor for the active catalyst, and substituting THF solvent with 2-MeTHF.

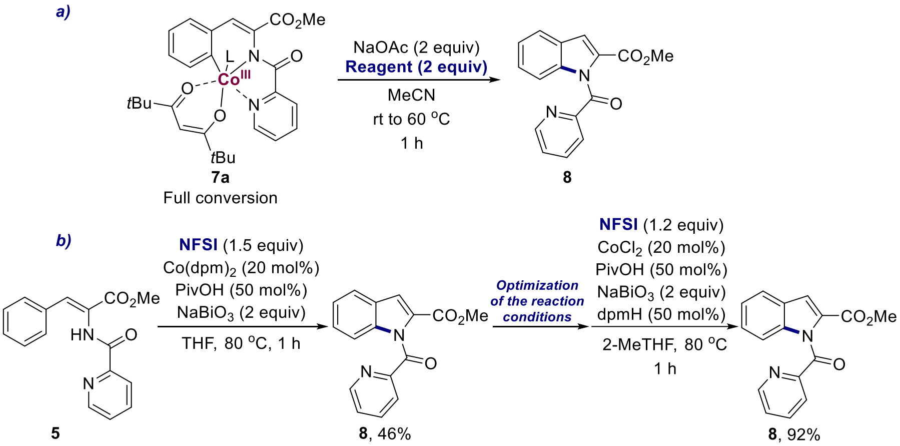


Fig. 6. The reactivity of cobaltacycle **7a** and optimization of reaction conditions.

After optimization, we tested the compatibility of the different functional groups with the optimized reaction conditions (Fig. 7). We observed that electron donating groups in the benzene ring moiety such as alkyl, alkoxy and phenyl in different positions gave the corresponding products in very good to excellent yields (products **8b**, **8c**, **8h**, **8k**, **8l**, **8n**, **8o**, **8q**). Halogenated products at the *ortho*- or *para*-positions generally formed well with yields from 50 % to 84 % (products **8d-8g**, **8m**, **8r**). Interestingly, electron-poor substrates containing 4-NO_2 and 4-CN groups did not deliver the desired products. 2-Naphthalene substituted substrate **5s** gave product **5s** with 76 % yield as a single regioisomer. Additionally, *meta*-substrates (**5n**, **5p**, **5u**) gave corresponding products with good yields (76 %, 95 %, 70 %) with the more sterically accessible C-H bond being activated.

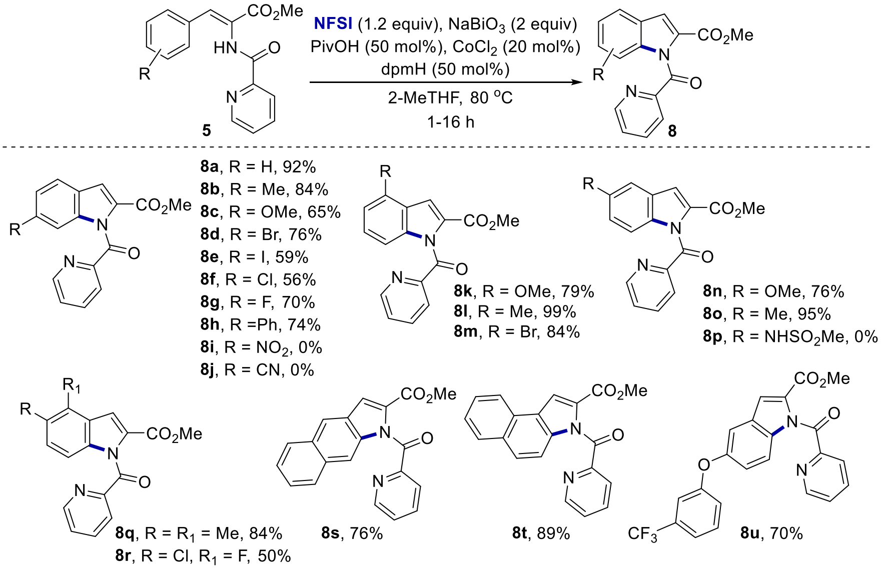


Fig. 7. Substrate scope for intramolecular amidation.

The application of the developed methodology was demonstrated by the synthesis of Atevirdine – a drug that has been extensively studied as an anti-HIV pharmaceutical (Fig. 8).[17]

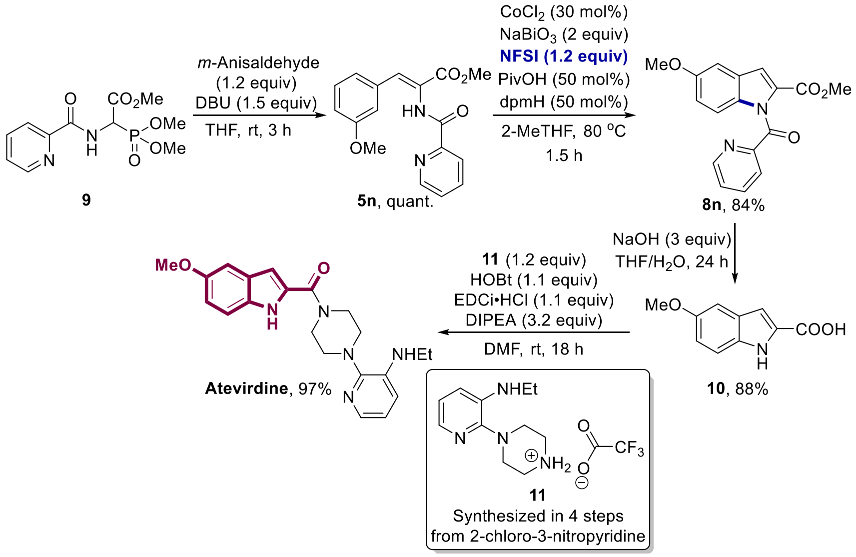
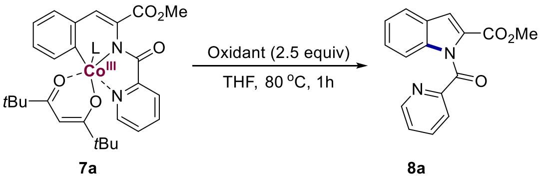


Fig. 8. Synthesis of Atevirdine using cobalt-catalyzed reaction as the key step.

The synthesis was carried out starting from *m*-anisaldehyde in four steps. Initially, *Horner–Wadsworth–Emmons* olefination yielded α-amidoacrylate **5n**, which was subjected to intramolecular amidation conditions to deliver indole carboxylate **8n** in 84 % yield. Subsequently, the picolinamide directing group was removed along with ester hydrolysis under basic conditions, yielding 5-methoxy indole carboxylic acid **10** with great yield (88 %). Finally, amide bond formation with piperazinium trifluoroacetate **11**, which was obtained in four steps from commercially available 2-chloro-3-nitropyridine, afforded atevirdine with almost quantitative yield.

To understand the reaction mechanism, additional mechanistic experiments were carried out. We envisioned that the reaction could proceed through the Co(IV) intermediate. To confirm it, we tried to synthesize indole **8a** from Co(III) complex **7a** in the presence of different organic and inorganic oxidants (Fig. 9), (Table 1).



7a
L = THF

8a

Fig. 9. Synthesis of indole **8a** from Co(III) complex **7a** with various oxidants.

Table 1

Indole **8a** Yield from Cobaltacycle **7a** with Various Oxidants

Entry	**Oxidant**	**NMR yield, %**
1	$PhI(OAc)_2$	33
2	$PhI(OCOCF_3)_2$	79
3	IBX	-
4	CAN	90
5	Ag_2CO_3	-
6	$NaBiO_3$ (2 equiv) + NFSI (1.2 equiv)	52
7	$NaBiO_3$	-
8	NFSI	76
9	$Mn(OAc)_3$•$2H_2O$	15
10	Without oxidant	-
11	Benzoquinone	-

From the results obtained, we concluded that the formation of indole derivatives occurs only in the presence of a strong oxidant. Additionally, we hypothesized that in the reaction media, there was initially a Co(IV) intermediate forming from Co(III) complex **7a**, which then undergoes reductive elimination to deliver indole, as the reductive elimination step is more favorable from the higher oxidation state of the metal.

Then we performed an intramolecular amidation reaction under the standard reaction conditions by substituting $Co(dpm)_2$ catalyst with $Co(dpm)_3$ in the absence of $NaBiO_3$ and observed that substrate **5a** was unreactive (Fig. 10 a). This result indicated that the first step of the catalytic cycle is Co(II) coordination to the substrate **5a** and not the Co(II/III) oxidation. Then, H/D scrambling experiments were conducted (Fig. 10 b). Employing THF-d_8 as the solvent and deuterated acetic acid instead of pivalic acid at incomplete conversion, we observed < 5 % H/D scrambling in the *ortho*-position of both the substrate and product. This result indicated that C-H bond activation is an irreversible process. Additionally, to confirm the intermediacy of cobaltacycle **7a**, we conducted an experiment employing cobalt complex **7a** as the reaction catalyst under the standard reaction conditions (Fig. 10 c). In these reaction conditions, we observed the formation of indole in 77 % yield.

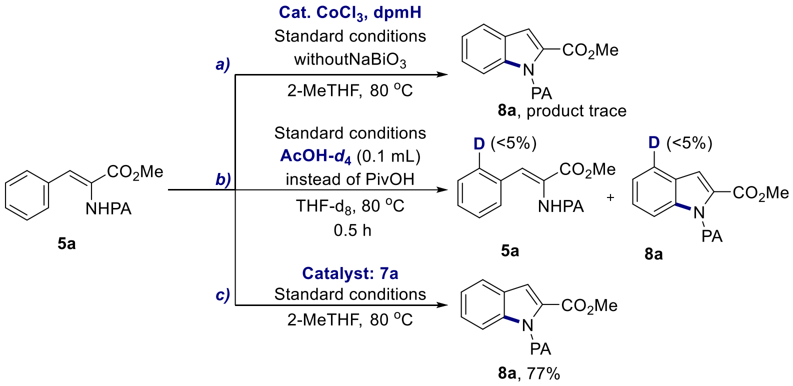


Fig. 10. Mechanistic control experiments.

To additionally confirm the oxidation potential and possibility of cobalt being oxidized to Co(IV), cyclic voltammetry experiments were conducted. In Fig. 11, the cyclic voltammogram for Co(III) complex **7a** at 0 °C temperature is shown with voltage up to 1 V. Below 0 V, the reduction of Co(III) to Co(II) did not occur, supporting the stability of the C-H activated cobaltacycles **7a**. On the other hand, approximately at $E_{\max}^{\mathrm{ox}} = 0.84\ V,$ a quasi-reversible redox event was observed for Co(III/IV), which is consistent with known literature reports.[18]

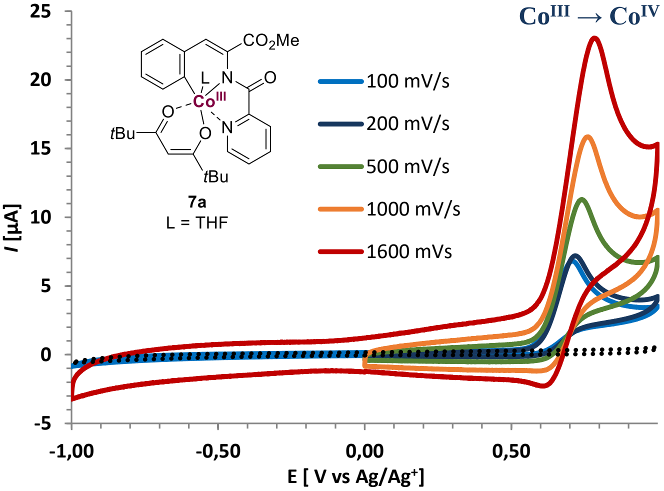


Fig. 11. CV of Co(III) complex **7a** at 0 °C up to 1 V.

Interestingly, the CV of Co(III) intermediate performed at room temperature and recorded from 0 to 1.8 V at different scan rates, showed three irreversible redox events (Fig. 12). The first redox event was assigned to the Co(III/IV) redox couple.

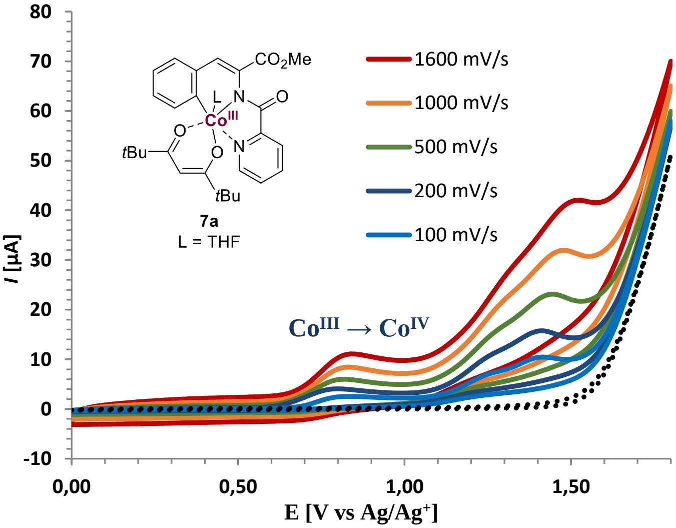


Fig. 12. Full CV of Co(III) complex **7a** at rt.

The observed irreversibility indicated that cobaltacycle **7a** was transformed into product **8a** upon oxidation, suggesting that intramolecular amidation could be achieved in an electrosynthetic pathway.[19] We confirmed the indole formation under CV conditions by comparing CVs of Co(III) complex **7a** and indole **8a** (Fig. 13).

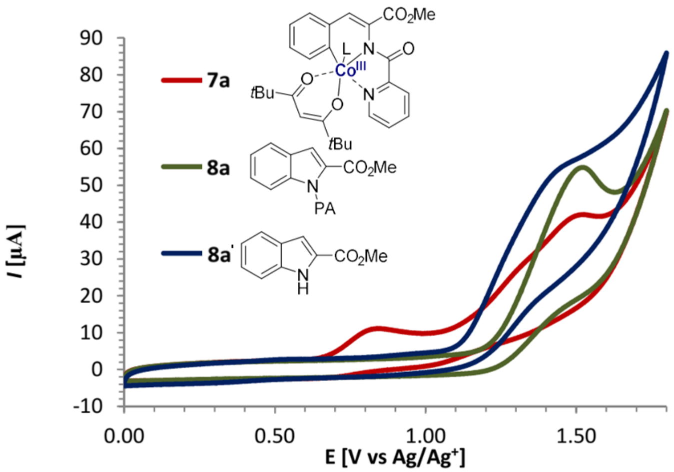


Fig. 13. CVs of Co(III) complex **7a**, indole **8a**, and indole with cleaved PA **8a’**.

Unfortunately, the third redox event remained unidentified. We hypothesized that the picolinamide directing group could be cleaved under the conditions of CV experiments. Therefore, using a mixture of zinc and acetic acid in ethanol, we achieved selective cleavage of the picolinamide moiety, affording indole-2-carboxylate **8a'** in good yield (Fig. 14). The CV of the indole derivative **8a'** showed a match to the unknown redox event.

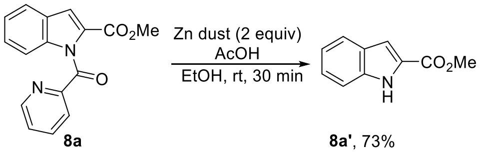


Fig. 14. Selective cleavage of the picolinamide directing group.

To explore the correlation between the electronic properties of substituents in α-amidoacrylates **5**, we conducted CV experiments for previously synthesized Co(III) complexes **7a**-**d** containing electronically different substituents (Fig. 15).

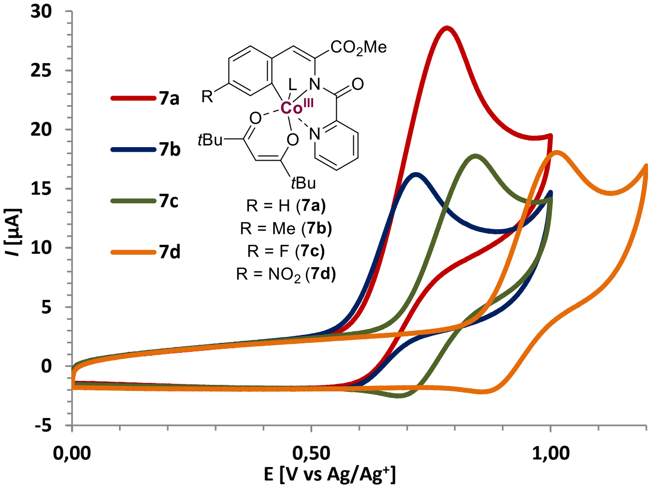


Fig. 15. CVs of cobalt complexes **7a-7d**.

The obtained results explain the lower reactivity of electron withdrawing group-containing substrates **5**, which could be associated with the increased oxidation potential of the corresponding Co(III) complex intermediates.

Based on our mechanistic experiments, we proposed a plausible reaction mechanism (Fig. 16).

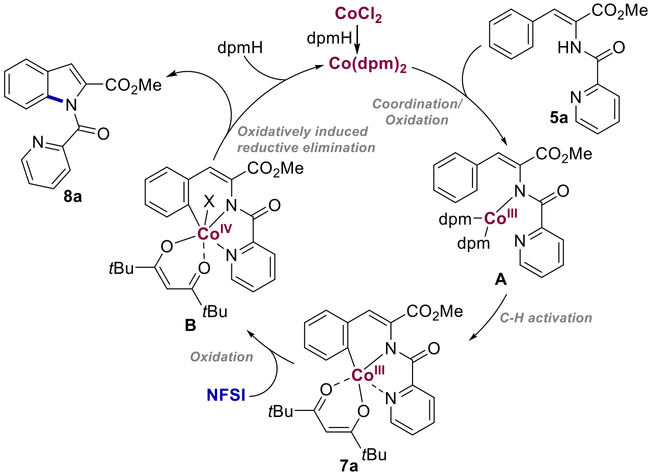


Fig. 16. Plausible reaction mechanism for intramolecular amidation of α-amidoacrylates.

Initially, the active catalyst Co(dpm)$_2$ is formed from CoCl$_2$ and the dpmH ligand. Then Co(II) catalyst is coordinated with the substrate **5a** and oxidized to Co(III) with NaBiO$_3$, forming intermediate **A**, which, upon the activation of the C-H bond, delivers cobaltacycle **7a**.

Afterwards, NFSI oxidizes cobaltacycle **7a** to Co(IV) intermediate **B**, which undergoes reductive elimination to deliver the final product **8a**. Alternatively, the transformation from **7a** to **8a** is called the oxidatively induced reductive elimination. Finally, as a result of ligand exchange, Co(II) is returned to restart the catalytic cycle.

2. Cobalt-catalyzed synthesis of 3-benzazepines

Further investigating the reactivity of the cobalt cycle **7a**, we found that the formation of 3-benzazepine **13a** can be observed using CaC_2 as a reactant (Fig. 17). It should be noted that starting from cobalt complex **7a**, complete consumption of the starting material was observed, and only one product, compound **13a**, was selectively obtained.

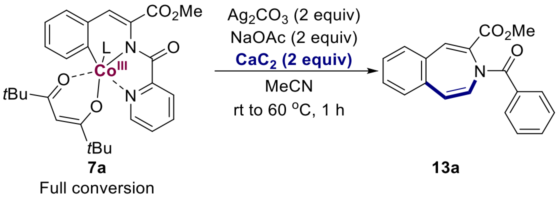


Fig. 17. Synthesis of benzazepine **13a** from Co(III) complex **7a**.

In industry, calcium carbide is being used to produce acetylene gas on a large scale. The synthesis of acetylene occurs according to the chemical equation:

$$CaC_2 + 2H_2O \rightarrow C_2H_2 + Ca(OH)_2.$$

Even though there are many known methods in the literature using calcium carbide in transition metal-catalyzed reactions, there are no examples in the literature where CaC_2 has been used in directed C-H bond activation and functionalization reactions as a source of acetylene gas. In addition, 3-benzazepines are common fragments in various drugs, natural substances and alkaloids (Fig. 18), such as the alkaloids – cephalotaxine,[20] bulgaramine,[21] turkiyenine,[22] antiobesity drug lorcaserin, and the bradycardic agent zatebradine.[23, 24]

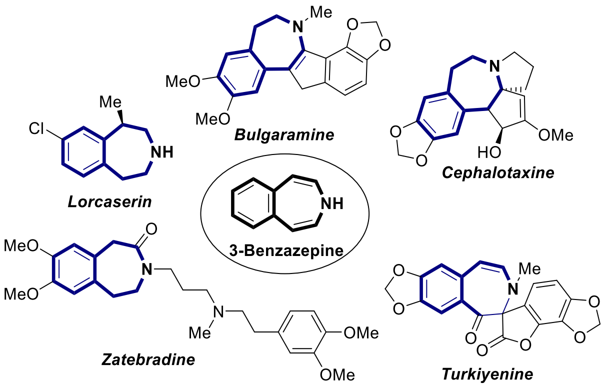


Fig. 18. 3-Benzazepine motif in drugs and natural compounds.

Since direct C-H bond activation and functionalization reactions using CaC_2 as the acetylene source were previously unknown, we decided to investigate and develop this transformation using cobalt catalysis.

For the optimization of reaction conditions, we chose α-amidoacrylate **5a** as a model substrate (Fig. 19). A broad scope of Co(II) catalysts, oxidants, basic/acidic additives, as well as solvents and temperature range were screened to find the optimal reaction conditions. Initially, we observed the formation of a product with a 21 % yield using calcium hypochlorite as an oxidant. After a series of control experiments, we managed to increase the NMR yield of the product to 99 %, employing $CoCl_2$/dpmH catalyst system, $NaBiO_3$ as an oxidant, $NaHCO_3$ as an additive and isobutyric anhydride as a ligand. Several C-H bond functionalization reactions are known where the addition of an anhydride additive significantly improved the product yield. This might be explained by the fact that the anhydride acts as a ligand for the metal catalyst in a specific step of a catalytic cycle, thus accelerating the transformation.[25]

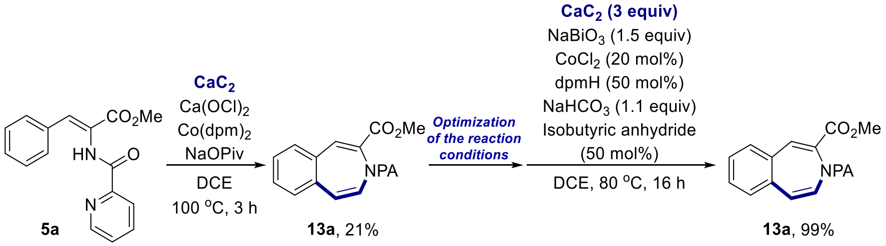


Fig. 19. Optimization of the reaction conditions.

After optimization of the reaction conditions, we switched our attention to the investigation of a substrate scope (Fig. 20). Under optimized reaction conditions, we were able to isolate benzazepine **13a** in 97 % yield. Moreover, upscaling the reaction to a gram-scale led to similar results without loss of efficiency, giving product **13a** in 96 % yield. Next, we investigated the impact of substituents on the reactivity and reactions' regioselectivity. Substrates with *ortho*-, *meta*- and *para*-substitution patterns gave the corresponding product in good to excellent yields. Using *meta*-substituted substrates **5f-h**, we observed high regioselectivity, and benzazepines **13f-h** arising from C-H bond functionalization of the less hindered C-H bond were obtained. Under optimized reaction conditions, excellent compatibility of electronically different substituents was observed – electron-rich substrates with methyl group (**5b**, **5j**) and methoxy (**5i**, **5k**), as well as electron-deficient substrates with cyano (**5d**) and nitro (**5o**) groups, gave the corresponding products generally in good yields. Additionally, halogenated products were obtained in 78 % to 99 % yields (products **13c**, **13e**, **13p-r**).

The structure of product **13c** was unambiguously confirmed by a single-crystal X-ray analysis. Sterically hindered substrates **5e** and **5i** gave the corresponding products **13e** and **13i** in very good yields (83 % and 79 %). Interestingly, substrates containing protected amino group moieties perfectly tolerated the annulation reaction conditions, giving access to products **13f** and **13g** in great yields. We also demonstrated that both 1- and 2-naphtalenyl amidoacrylates

5s and **5t** were reactive under the reaction conditions, and naphtoazepines **13s** and **13t** were obtained.

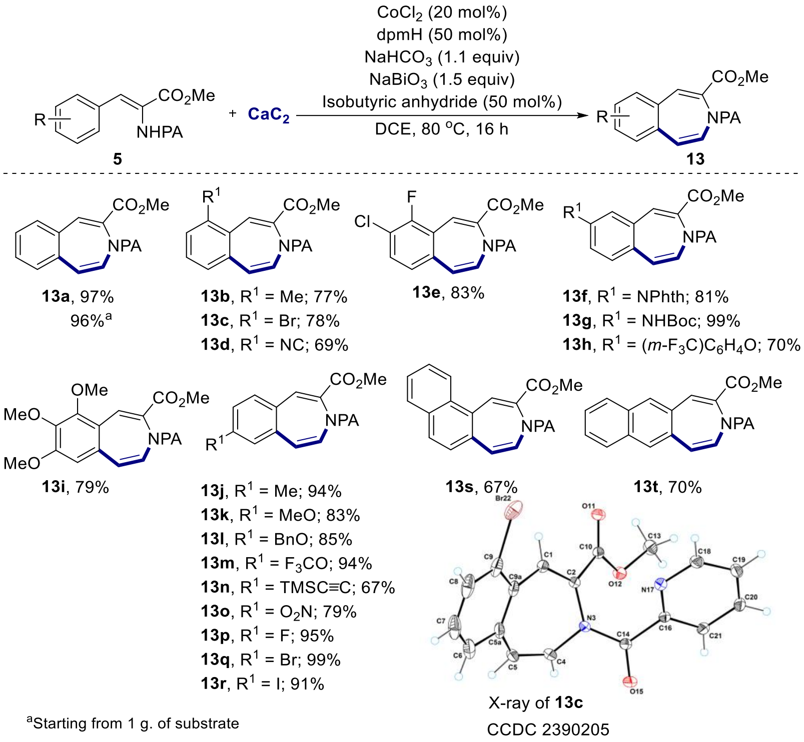


Fig. 20. Substrate scope for Co-catalyzed annulation with CaC_2.

In order to gain insight into the reaction mechanism, additional control experiments were performed. First, cobaltacycle **7a** was detected in the reaction mixture by HRMS analysis (Fig. 21 a). Employing the previously developed method, we synthesized Co(III) complex **7a** and confirmed its intermediacy in the reaction. Stoichiometric experiments using Co(III) complex **7a** as substrate were analyzed at incomplete conversion without (Fig. 21 b) and in the presence of isobutyric anhydride (Fig. 21 c) to determine the role of isobutyric anhydride as a potential ligand for cobalt intermediates. The obtained results indicated that in the presence of anhydride, the reaction is slightly accelerated. We concluded that isobutyric anhydride most probably serves as a ligand after C-H bond activation, accelerating the reductive elimination step or acetylene migratory insertion. Employing cobalt complex **7a** as a reaction catalyst (Fig. 21 d), benzazepine **13a** was obtained in 89 % yield, which was determined by ^{1}H-NMR.

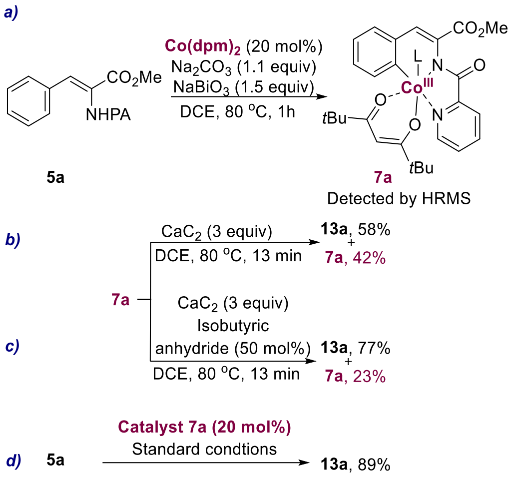


Fig. 21. Mechanistic investigations.

Based on our mechanistic experiments and literature precedents, the possible reaction mechanism is depicted in Fig. 22.

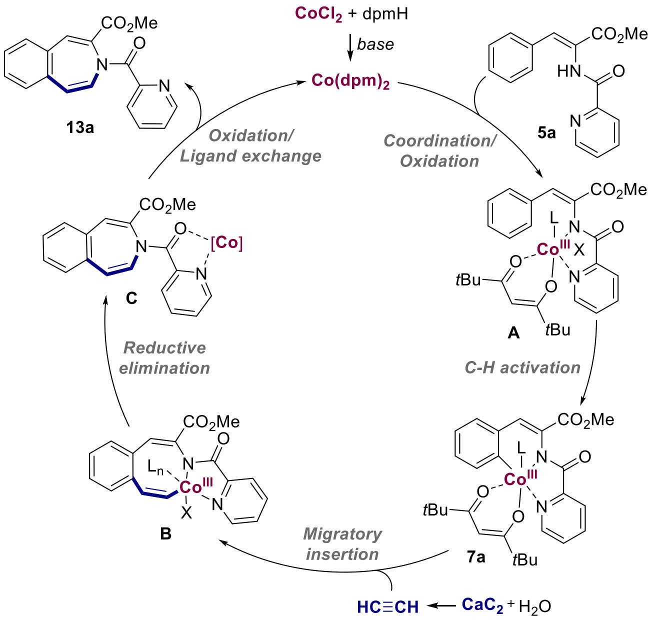


Fig. 22. Plausible mechanism for cobalt-catalyzed 3-benzazepine formation.

At first, the active Co(dpm)$_2$ catalyst is formed from CoCl$_2$ and dpmH ligand in the presence of base. Then, Co(II) coordinates to the substrate, and after oxidation/C-H bond activation sequence, cobaltacycle **7a** is formed. It is not excluded that cobaltacycle **7a** undergoes ligand exchange from dpm to isobutyric anhydride prior to alkyne migratory insertion. Afterwards, acetylene gas coordination and migratory insertion deliver cobalt complex **B**, which, after reductive elimination, furnishes **C**. Finally, after demetalation, intermediate **C** product **13a** is formed, and cobalt is reoxidized to restart the catalytic cycle.

3. Cobalt-catalyzed sulfonamide and benzamide C-H bond annulation

As the next step of our study, we chose to transfer the C-H bond annulation methodology with calcium carbide to benzenesulfonamide derivatives. Since 2015, several sulfonamide annulations have been reported, including reactions with alkynes or allenes as annulation reagents,[26–30] as well as an impressive method for atroposelective annulation has been developed (Fig. 23).[31] Despite the notable progress over the last ten years in the field of sulfonamide C-H bond annulation, the methodology lacks examples of C3/C4 unsubstituted benzosultam synthesis. We envisioned that sulfonamides would react similarly to α-amidoacrylates with CaC_2, giving access to unsubstituted benzosultams under cobalt catalysis.

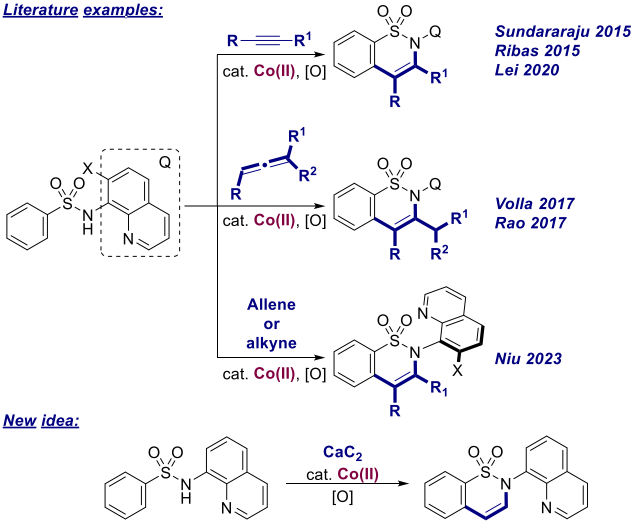


Fig. 23. Different approaches towards sulfonamide C-H bond annulations.

For the optimization study, we used *p*-toluenesulfonamide **14a** with 8-aminoquinoline directing group (Fig. 24).

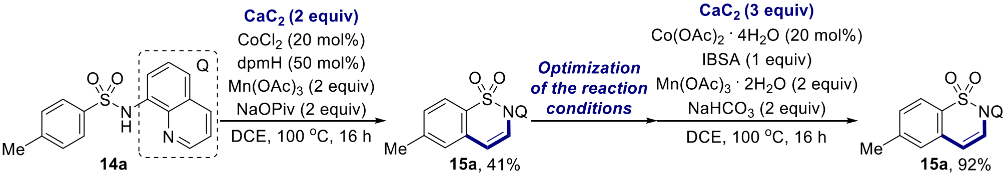
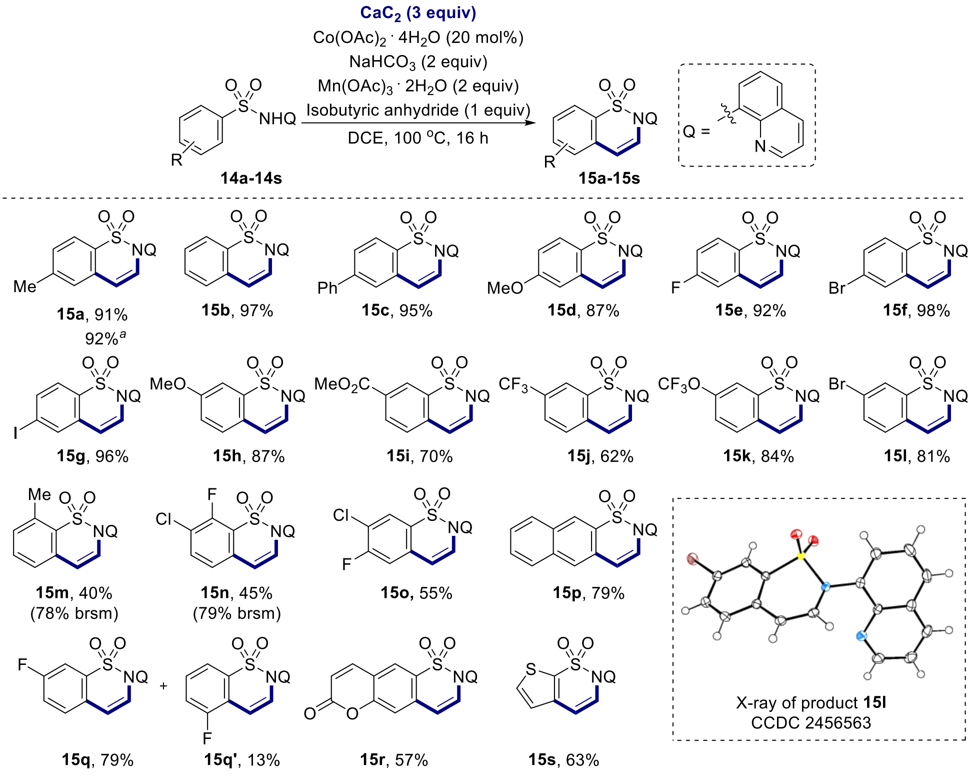


Fig. 24. Optimization of the reaction conditions for sulfonamide **14a** annulation.

During optimization we found that the best result can be achieved by employing the following catalytic system: $Co(OAc)_2 \cdot 4H_2O$ catalyst, $NaHCO_3$ additive, $Mn(OAc)_3 \cdot 2H_2O$ oxidant, isobutyric anhydride ligand in DCE solvent at 120 °C temperature.

Next, we investigated the compatibility of various functional groups with the optimized reaction conditions (Fig. 25). We observed that sulfonamides **14a-14s** with *ortho*-, *meta*- and *para*-substitution patterns well tolerated the reaction conditions, giving access to the corresponding products in good to excellent yields (40–99 %).



[a]*Starting from 1 g of substrate*

Fig. 25. Sulfonamide **14** scope for cobalt-catalyzed annulation with CaC_2.

Electron-donating groups like alkyl (products **15a**, **15m**), alkoxy (**15d**, **15h**), phenyl (**15c**) and electron-withdrawing groups such as trifluoromethyl (**15j**), trifluoromethoxy (**15k**), and methyl ester (**15i**) in the benzene ring moiety gave annulation products smoothly. Methyl-substituted substrate **14a** and unsubstituted substrate **14b** gave the corresponding products in great yields – 91 % and 97 %. Moreover, upscaling the reaction to a 1-gram scale did not impact the yield of **14b**. Halogenated products **15e**, **15f**, **15g** and **15l,** as well as dihalogenated products **15n** and **15o,** formed in medium to excellent yields (up to 98 %). It is worth mentioning that *meta*-substituted substrates gave corresponding products **15h-15l** in good yields (62–99%) and were isolated as single regioisomers. Interestingly, 3-fluorobenzenesulfonamide **14q** was also a competent substrate for annulation with CaC_2, although in this case the reaction was not as selective and both regioisomers – **15q** (79%) and **15q’** (13%) – were isolated.[32] Sterically hindered *ortho*-substituted substrates **14m** and **14n** delivered corresponding products **15m** and **15n** in mediocre yields (40 % and 45 %, respectively). In this case, low yields can be explained by the low reactivity of the corresponding starting materials. Naphthyl sulfonamide **14p** also demonstrated good reactivity, forming **15p** in 79 % yield as a single regioisomer. Additionally, heterocyclic sulfonamides **14r** and **14s** were suitable substrates for the annulation reaction, furnishing products **15r** and **15s** in good yields.

Inspired by the fact that sulfonamides **14** successfully underwent annulation with calcium carbide, we decided to apply this method for benzamide substrates **16** (Fig. 26). Pleasingly, we observed the formation of the corresponding product under standard reaction conditions, and no additional modifications or optimizations were required.

We observed that different functional groups were compatible with the reaction conditions. Electron-rich benzamides (products **17a**, **17g**), electron-poor benzamide (**17c**), as well as electron-neutral or halogen group-containing benzamides (products **17b**, **17d**) participated in the annulation reaction and gave the desired products in very good to great yields (78–93 %). Unfortunately, *meta*-methoxy and methyl ester functionalities containing benzamides delivered the corresponding products as a mixture of inseparable regioisomers. Despite that, the regioisomer ratio was rather acceptable, and the yields of products **17e** and **17f** were 74 % and 68 %, respectively. In contrast to benzosultams, *ortho*-substituted product **17h** was obtained in good yield – 69 %. Additionally, two heterocyclic amides were subjected to C-H bond functionalization with calcium carbide. As a result, thienopyridinone **17i** was obtained in 62 % yield, while furopyridinone **17j** was isolated in only 27 % yield. We found that in this case, the low yield is due to the low conversion of the starting material.

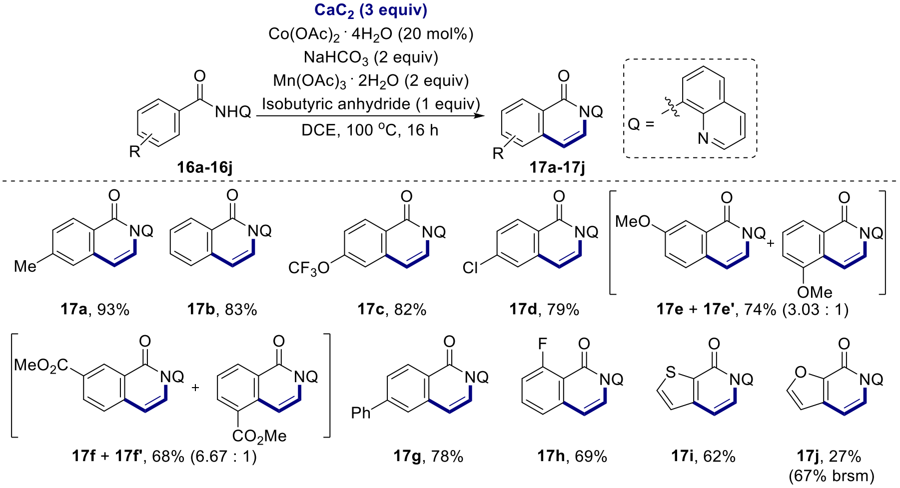


Fig. 26. Benzamide **16** scope for cobalt-catalyzed annulation with CaC_2.

While studying the substrate scope for the developed method, we found some limitations (Fig. 27). Substrates such as sulfinamide **18** or phosphinic amide **19** were unstable under the reaction conditions, and only product trace along with a large amount of decomposition by-products were observed. On the other hand, isobutyramide **20** did not participate in the annulation reaction, which could be explained by the fact that harsher reaction conditions are required for activation and functionalization of the C(sp^3)-H bond.

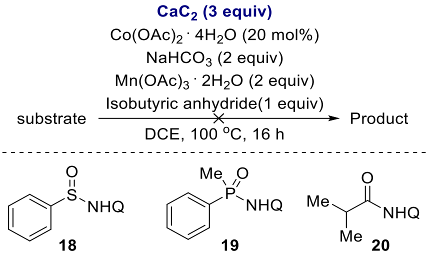


Fig. 27. Unsuccessful substrates for C-H bond annulation.

It has recently been reported and discussed in detail that two types of catalytic cycle might be operative for aminoquinoline-directed cobalt-catalyzed C-H bond functionalization reactions – Co(I)/Co(III) and through Co(IV).[33] Based on previous reports from our group[11, 14, 15, 34] and relevant literature precedents,[18, 19, 26–30, 35] it is very unlikely that a catalytic cycle involving Co(IV) intermediate is operative in our case. Based on these examples, we propose a plausible reaction pathway *via* the Co(I)/Co(III) catalytic cycle (Fig. 28).

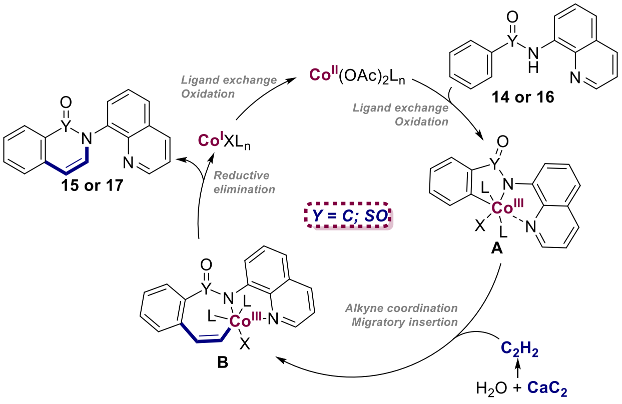


Fig. 28. Plausible reaction mechanism for sulfonamide/benzamide annulation.

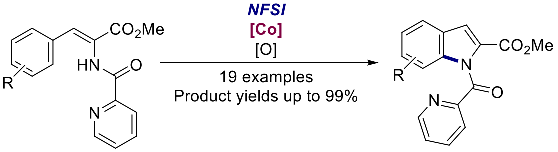
Initially, Co(II) catalyst is coordinated to sulfonamide **14** or benzamide **16**, and then oxidation/C-H bond activation sequence provides cobalt complex **A**. Migratory insertion of acetylene gas delivers cobaltacycle **B**, which after reductive elimination yields sultam **15** or isoquinoline **17** along with Co(I) species. Oxidation and ligand exchange returns Co(I) species back to the catalytic cycle.

Within the Thesis, a novel cobalt-catalyzed intramolecular amidation reaction was developed. Using α-amidoacrylate derivatives **5** as substrates, we were able to obtain indole products **8** bearing various substituents in the benzene ring moiety. The developed reaction was also successfully applied for the synthesis of the anti-HIV drug Atevirdine. Based on the synthesis of reaction intermediates, control experiments, and cyclic voltammetry studies we proposed the plausible reaction mechanism *via* the formation of Co(IV) intermediate in the reaction media.

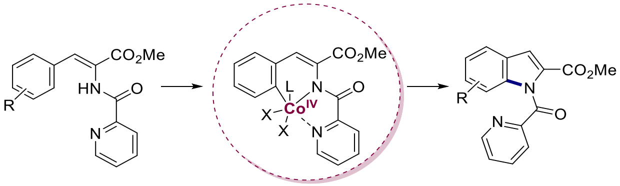
In addition, two new cobalt-catalyzed C-H annulation methodologies were developed, employing α-amidoacrylate **5**, sulfonamide **14**, and benzamide **16** derivatives. In these newly developed protocols, we used calcium carbide for the generation of the acetylene gas *in situ*. A thorough examination of the substrate scope was conducted, and possible reaction mechanisms were proposed based on the literature precedents and our mechanistic control experiments.

CONCLUSIONS

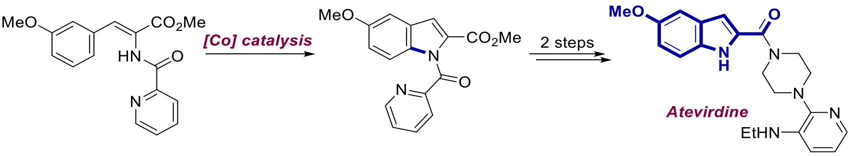
1. Under cobalt catalysis, α-amidoacrylate derivatives can be transformed to indole-2-carboxylate derivatives *via* intramolecular amidation using picolinamide as a directing group.



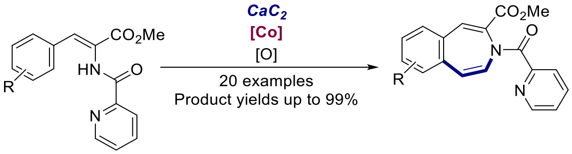
2. Based on control experiments, cyclic voltammetry studies and DFT calculations, it was unambiguously proved that intramolecular amidation of α-amidoacrylate derivatives proceeds through oxidatively induced reductive elimination pathway involving Co(IV) species.



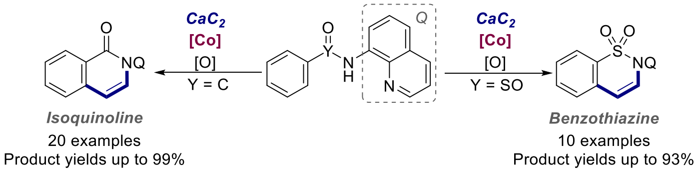
3. The developed method for intramolecular amidation can be successfully applied for the synthesis of atevirdine – an anti-HIV drug, as well as its analogues starting from commercially available substituted aldehydes.



4. 3-Benzazepine derivatives can be efficiently obtained *via* cobalt-catalyzed C-H bond annulation of α-amidoacrylates using calcium carbide as the acetylene gas source.



5. Benzosultam and isoquinoline derivatives can be efficiently obtained *via* cobalt-catalyzed C-H bond annulation of corresponding aryl sulfonamides and benzamides using calcium carbide as the acetylene gas source.



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PIELIKUMI/PUBLICATIONS

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Inorganics **2023**, *11*, 194.

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Review

Co(III) Intermediates in Cobalt-Catalyzed, Bidentate Chelation Assisted C(sp^2)-H Functionalizations

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Abstract: The C-H bond activation and functionalization is a powerful tool that provides efficient access to various organic molecules. The cobalt-catalyzed oxidative C-H bond activation and functionalization has earned enormous interest over the past two decades. Since then, a wide diversity of synthetic protocols have been published for C-C, C-Het, and C-Hal bond formation reactions. To gain some insights into the reaction mechanism, the authors performed a series of experiments and collected evidence. Several groups have successfully isolated reactive Co(III) intermediates to elucidate the reaction mechanism. In this review, we will summarize information concerning the isolated and synthesized Co(III) intermediates in cobalt-catalyzed, bidentate chelation assisted C-H bond functionalization and their reactivity based on the current knowledge about the general reaction mechanism.

Keywords: cobalt; C-H bond functionalization; Co(III) intermediate

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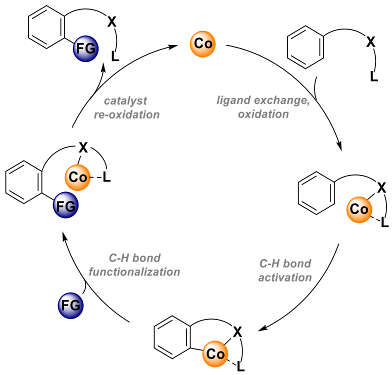
1. Introduction

The directed C-H bond functionalization methodology using transition metal catalysis has proven itself as a valuable organic synthesis tool [1–8]. Nowadays, using the directed C-H bond functionalization methodology, a diverse range of selective transformations can be achieved, including C-C, as well as C-O, C-N, C-Hal, C-S, etc. bond formation, allowing to obtain more complicated products from simple starting materials in step- and atom-economic fashion [1–8]. C-H bond functionalization using first-row transition metal catalysts recently has emerged not only as an attractive alternative to noble metals, but also as an opportunity to expand the scope of C-H bond functionalization methodology due to their unique reactivity [9]. Among other 3d elements, cobalt is considered to be a sustainable catalyst due to its price, biorelevance, earth abundance and lower toxicity. Since 2010, great progress in the development of novel methods using cobalt catalysis had been achieved [10–20]. In general, C-H bond functionalization using cobalt catalysis can be divided in two categories: low valent and high valent, depending on the catalyst used for cobaltation [21]. However, high valent cobalt catalysis can be divided in two main directions, reactions using Cp*Co(III) complexes as catalysts and reactions using simple Co(II) and Co(III) salts in combination with bidentate chelation assistance [18]. Herein, we will focus on last direction, which after pioneering work by Daugulis in 2014 [22] was proven to be efficient for wide range of C-H functionalizations [10–22].

2. General Mechanism for Cobalt-Catalyzed, Bidentate Chelation Assisted C-H Bond Functionalization

Over the last two decades, gathered mechanistic experiments and collected evidence provided a general idea of the operative mechanism in cobalt-catalyzed, bidentate chelation assisted C-H bond functionalization. According to the literature, it is believed that for the major part of the found transformations, the Co(II)-Co(III)-Co(I) catalytic cycle is operative [18,23]. The general mechanism is shown in Scheme 1, which consists of four elementary steps:

- ligand exchange (substrate coordination)/oxidation;
- C-H bond activation;
- C-H bond functionalization;
- catalyst re-oxidation to return active species in catalytic cycle [23].



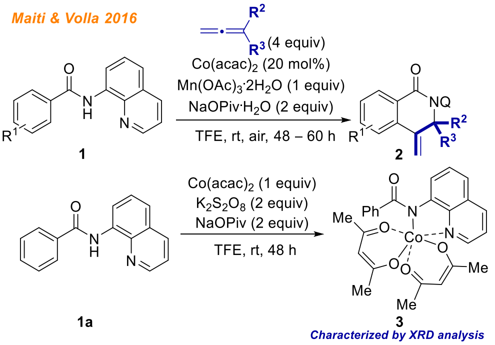
Scheme 1. General mechanism for the cobalt-catalyzed C(sp^2)-H bond functionalization [23].

To the date, several intermediate Co(III) complexes have been isolated. In this review, these species will be discussed in such order as they participate in the catalytic cycle.

3. Ligand Exchange, Oxidation

The first step of the catalytic cycle is ligand exchange/substrate coordination and oxidation of Co(II) species to Co(III) species. According to the literature data, two operative pathways are plausible for this step. First, the catalytic cycle could be initiated with substrate coordination to Co(II) salt to form a Co(II)-substrate complex, which is further oxidized to a Co(III) complex that undergoes the C-H activation step. In the second operative pathway, the Co(II) catalyst might be first oxidized to Co(III) salt. Next, substrate coordination takes place. In the literature, there is support for both of these pathways. Most likely, the operative pathway depends on the reaction conditions and/or substrate used for the transformation [23].

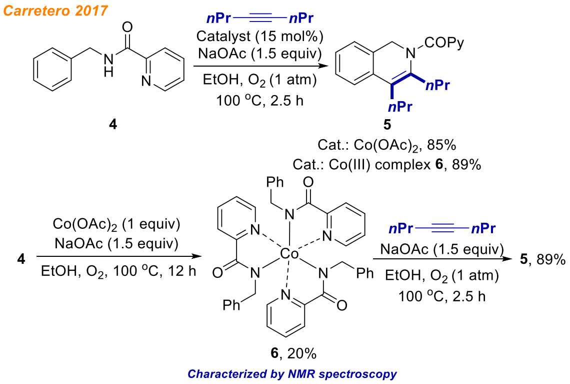
In 2016, Maiti and Volla reported a novel cobalt-catalyzed methodology for the intermolecular heterocyclization of benzamides **1** (Scheme 2) [24]. In their work, the following conditions were used: allene as the C-H bond functionalization reagent, $Co(acac)_2$ as the catalyst, $Mn(OAc)_3{\cdot}2H_2O$/air as reaction oxidant, and sodium pivalate in TFE. Using the developed methodology, authors were able to provide a broad substrate scope with respect to both allenes and benzamides, delivering 41 different products with yields up to 90%. The authors conducted series of mechanistic experiments to study the reaction mechanism in detail. The authors concluded that electrophilic cobaltation is unlikely based on competitive experiments between methoxy- and fluoro-substituted benzamides. Experiments with deuterium labeled substrates indicated that C-H bond activation might not be the rate-limiting step. Additionally, authors were able to isolate cobalt(III)-benzamide intermediate **3**, whose structure was confirmed with XRD analysis. Along with complex **3**, authors detected the formation of C-H activated Co(III)-intermediate by HRMS, although they were not able to isolate corresponding complex. Based on the mechanistic experiments as well as isolated complex **3**, the authors proposed the plausible reaction mechanism, which is consistent with the general Co(II)-Co(III)-Co(I) catalytic cycle.


Maiti & Volla 2016

Characterized by XRD analysis

Scheme 2. Cobalt-catalyzed benzamide **1** cyclization with allenes [24].

In 2017, the Carretero group reported an efficient protocol for the cobalt-catalyzed, picolinamide-directed C-H bond functionalization/annulation of benzylamine derivatives **4** with various alkynes (Scheme 3) [25]. The reaction proceeds in the presence of $Co(OAc)_2$ catalyst, O_2 oxidant, and NaOAc additive in EtOH at 100 °C temperature. The authors were able to ensure good functional group tolerance under the reaction conditions as well as a variety of terminal and internal alkynes delivered the desired products **5** predominantly with good and excellent yields. According to the mechanistic hypothesis, the authors propose that this reaction proceeds through the octahedral cobalt intermediate **6**, which was successfully isolated. The structure of Co(III) complex **6** was proven by ESI-HRMS and NMR analysis, although no crystals for X-ray diffraction analysis were obtained. In the stoichiometric experiment, Co(III)-species **6** reacted with 4-octyne to afford product **5** in 89% yield. Moreover, Co(III) complex **6** was found to be catalytically competent in the reaction of **4** with alkyne, delivering product **5** in 89% yield. In comparison, under the standard reaction conditions using $Co(OAc)_2$ salt, the same product **5** was obtained in 85% yield. These results indicated that complex **6** could be the active catalyst precursor for the transformation. Additionally, the authors performed ESI-HRMS experiments of the reaction mixture to shed some more light on the reaction mechanism, and deciphered different cobalt complexes being present in the reaction mixture, although none of them was isolated and characterized.

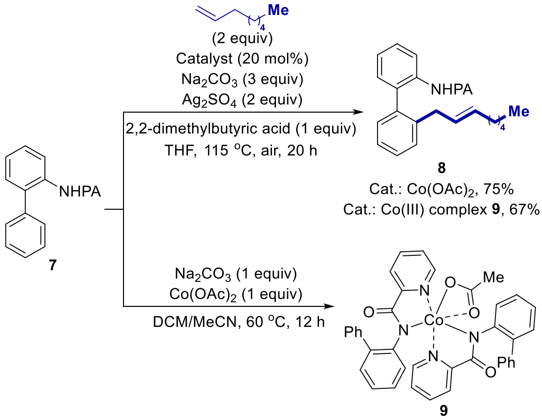

Carretero 2017

Characterized by NMR spectroscopy

Scheme 3. Cobalt-catalyzed C-H bond functionalization/annulation of benzylamine derivatives **4** [25].

Two years later, in 2019, Lahiri, Zanoni and Maiti reported a cobalt-catalyzed C-H bond allylation reaction using arylanilines **7** as substrates and unbiased terminal olefins (Scheme 4) [26]. The most common problem in these reactions is products' styrenyl/allylic regioselectivity of the double bond, which arises from the metal center's ability to unselectively perform β-hydride elimination. In this context, authors successfully overcame the challenge and were able to deliver 36 different aryl(allyl)anilines **8** with yields up to 96% in a highly selective fashion. In addition, the authors demonstrated that picolinamide directing group (PA) can be easily removed upon slight heating in basic conditions. To gain insight into the reaction mechanism, among kinetic and labeling studies, authors were able to isolate five-membered Co(III) intermediate **9**, whose structure was confirmed using XRD and ESI-MS analyses. The isolated Co(III) complex **9** was found to be catalytically competent, delivering product **8** in 67% yield, suggesting the involvement of a catalytically active high-valent Co(III) species.

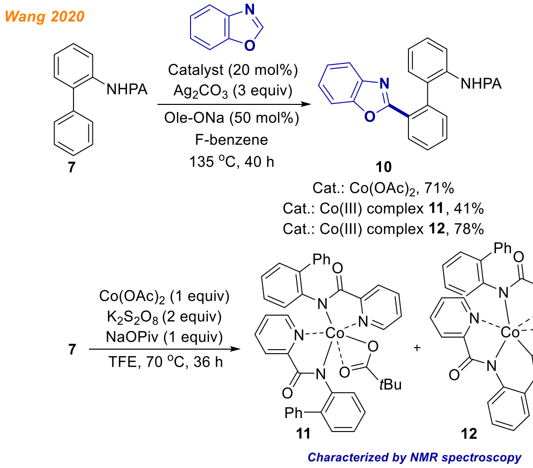
Lahiri, Zanoni & Maiti 2019



Characterized by XRD analysis

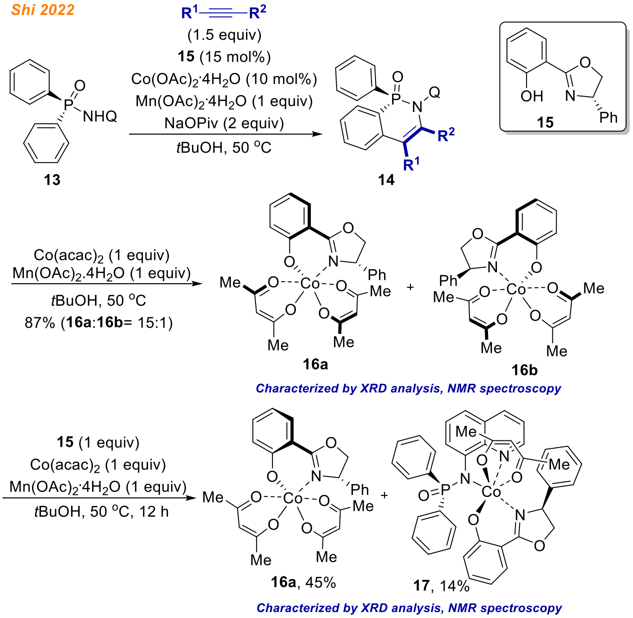
Scheme 4. Cobalt-catalyzed allylation of biphenyl amines **7** with terminal olefins [26].

In 2020, Wang and colleagues demonstrated a novel cobalt-catalyzed C-H/C-H bond cross-coupling reaction between benzoxazole and aryl aniline **7** (Scheme 5) [27]. The use of $Co(OAc)_2$ catalyst, Ag_2CO_3 oxidant, and Ole-ONa base in fluorobenzene was found to represent the optimal conditions for the successful reaction. The main advantage of the developed transformation was the straightforward access to biphenyls **10** in good yields (up to 73%), which possess antifungal activities and COX-2 inhibition potency. To investigate the reaction mechanism, the authors performed series of control experiments, including H/D exchange and KIE experiments, which led to conclusion that the C-H activation step is irreversible, but not the rate-determining step. Additionally, two Co(III) intermediates **11** and **12** were obtained by the reaction of aniline **7** with a stoichiometric amount of $Co(OAc)_2$, oxidant and base. Both Co(III) complexes **11** and **12** were characterized using NMR spectroscopy and high-resolution mass spectrometry. According to the suggested reaction mechanism, Co(III) complex **12** could be obtained from Co(III) complex **11** via a C-H activation step, which most likely occurs via a base-promoted concerted metalation-deprotonation mechanism. Notably, cobaltacycles **11** and **12** provided the desired product **8** in 41% and 78% yield, respectively, whereas using $Co(OAc)_2$ as the catalyst, the product yield was 71%, which confirmed the hypothesis that both isolated Co(III) complexes are most likely intermediates of the developed reaction.



Scheme 5. Cobalt-catalyzed synthesis of arylanilines **10** [27].

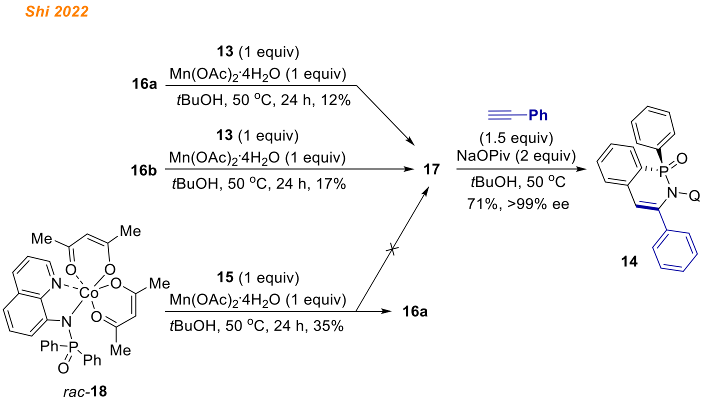
Recently, in 2022, the Shi group reported an elegant enantioselective C-H bond functionalization methodology exploiting diarylphosphinamides **13** (Scheme 6) [28]. In their study, employing $Co(OAc)_2{\cdot}4H_2O$ catalyst and Salox ligand **15**, azaphosphinines **14** were obtained with yields up to 99% with fascinating product enantioselectivities (up to >99% ee). The authors demonstrated great substrate/alkyne scope, delivering 45 different enantiopure products with excellent yields. Great emphasis was put on the understanding of the reaction mechanism and isolation of potential intermediates of the catalytic cycle.



Scheme 6. Cobalt-catalyzed enantioselective C-H functionalization of arylphosphinamides **13** [28].

First, to test the proof of concept, authors synthesized chiral octahedral Co(III)-Salox complexes **16**, which were hypothesized to act as the reaction catalysts. Accordingly, Co(acac)$_2$ in combination with Mn(OAc)$_2$·4 H$_2$O in the presence of chiral ligand **15** gave Co(III)-Salox complex diastereomers **16a** and **16b** (**16a**:**16b** = 15:1) in high yield.

With both Co(III) complex isomers **16a** and **16b** in hand, the authors proved their hypothesis and demonstrated that both complexes **16** are suitable chiral catalysts for enantioselective desymmetrizing C-H annulation of diarylphosphinamides **13** with alkynes thereby demonstrating the structure of the active cobalt catalyst which participates in developed reaction. Next, the reaction of diarylphosphinamide **13** with ligand **15** and Co(acac)$_2$ under oxidative conditions resulted in the simultaneous formation of Co(III) complexes **16a** and **17** with 45% and 14% yield, respectively. Additionally, both **16a** and its diastereomer **16b** in the reaction with diarylphosphinamide **13** in the presence Mn(OAc)$_2$·4H$_2$O gave Co(III) complex **17** (Scheme 7) [28]. The authors speculated that Mn(OAc)$_2$·4H$_2$O likely promotes the formation of **17** by facilitating ligand exchange, as without Mn(OAc)$_2$·4H$_2$O, complex **17** was not observed. In contrast, ligand exchange between the pre-formed *rac*-**18** and ligand **15** provided complex **16a**, not **17**. Finally, complex **17** in reaction with phenylacetylene gave product **14** in 71% yield, suggesting that all of the obtained cobalt complexes **16**–**18** might be the reaction intermediates.



Scheme 7. Mechanistic studies of the Cobalt/Salox-catalyzed synthesis of azaphosphinines **14** [28].

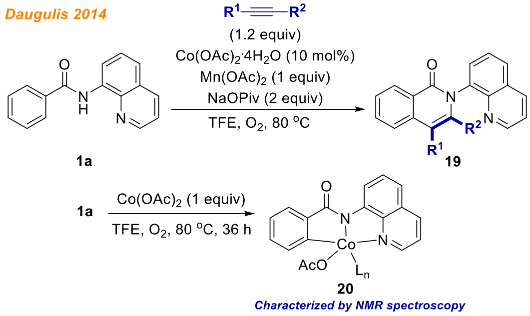
4. C-H Bond Activation

The key elementary step of C-H bond functionalization is the C-H bond activation. For high-valent cobalt catalysis, several C-H bond activation mechanisms leading to the formation of Co(III)-aryl complex are considered to be operative:

- electrophilic aromatic substitution;
- base-assisted intramolecular electrophilic substitution;
- concerted metalation–deprotonation;
- single-electron transfer [23,29].

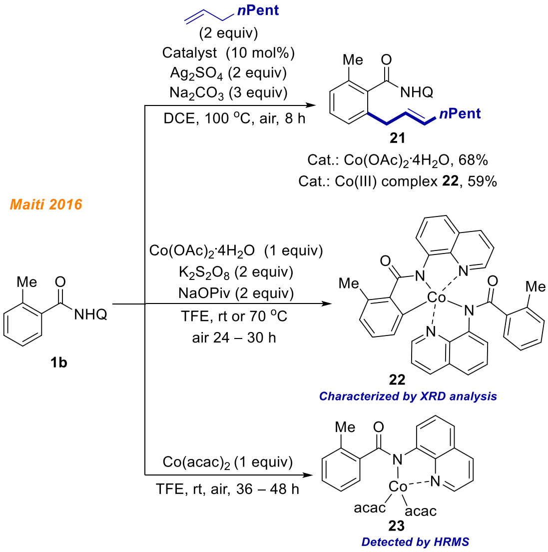
In the literature, there are several examples of isolated relatively stable Co(III)-aryl complexes obtained via direct C-H bond activation. Such complexes are proven to be invaluable assets for the mechanistic studies.

In early 2014, the Daugulis group developed benzamide **1a** C(sp^2)-H bond alkenylation with alkynes, using 8-aminoquinoline (Q) as a directing group (Scheme 8) [22]. The reaction conditions were mild and provided products **19** in good to excellent yields, tolerating a wide range of alkynes and substituents at benzene ring moiety. The authors hypothesized that due to the aminoquinoline stabilization of metals in high oxidation state, cobalt complex **20** could be the reaction intermediate. In addition, they successfully synthesized complex **20**, the structure of which was confirmed by NMR analysis, providing strong evidence for C(sp^2)-H bond activation of phenyl moiety and Co(III) species.



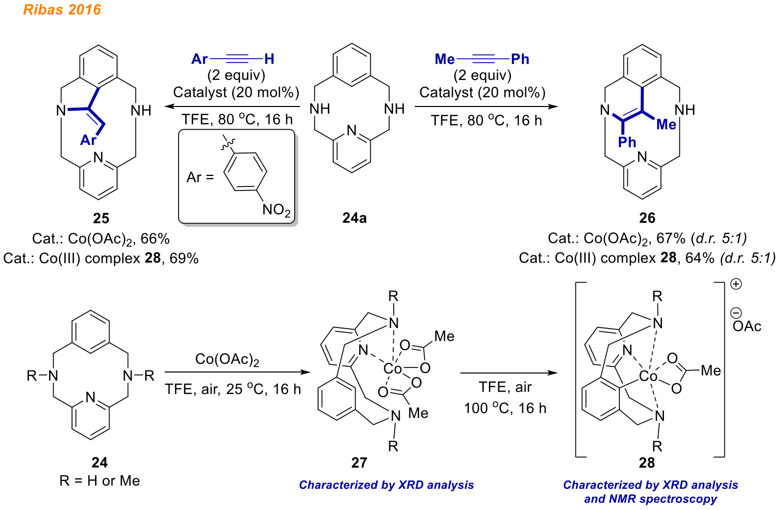
Scheme 8. Cobalt-catalyzed aminoquinoline-directed C(sp^2)-H bond alkenylation by alkynes [22].

Maiti and co-workers in 2016 disclosed a novel methodology for benzamide **1b** C(sp^2)-H bond allylation (Scheme 9) [30]. The optimization studies showed that the combination of $Co(OAc)_2 \cdot 4H_2O$ catalyst, Ag_2SO_4 oxidant, and 8-aminoquinoline directing group was the most suitable for the developed transformation. Both electron-donating and electron-withdrawing amides were successfully applied and yielded allylamides **21** with moderate to very good yields. In order to thoroughly outline all the aspects of this reaction, a series of control experiments were performed, including kinetic and labeling studies along with radical quenching experiments. Moreover, the authors succeeded in isolation of C-H activated Co(III)-aryl intermediate **22**, and proved its catalytic competency towards developed reaction. Employment of complex **22** as the catalyst yielded allylamide **21** in 59% yield. Additionally, they identified and characterized cobalt(III) complex **23** by HRMS, which underwent C-H bond activation/ligand exchange steps and formed Co(III)-aryl complex **22** after the addition of a stoichiometric amount of NaOPiv to the reaction mixture.



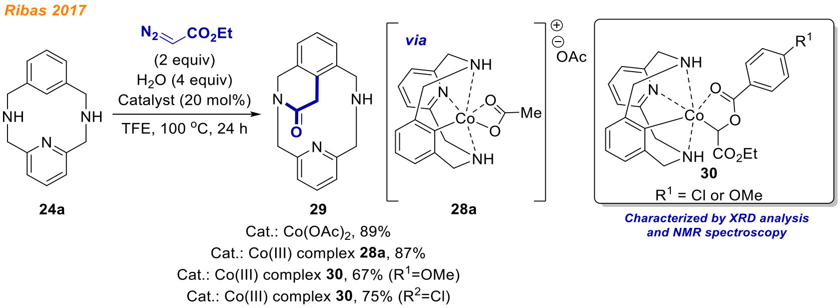
Scheme 9. Cobalt-catalyzed C-H bond allylation of benzamide derivatives **1b** [30].

In 2016, Ribas and co-workers described the synthesis and characterization of benchtop-stable organometallic aryl-Co(III) complexes obtained through C-H bond activation, using a 12-membered macrocyclic substrate **24a** (Scheme 10) [31]. Cobalt (II) coordination compounds **27** were prepared by the reaction of $Co(OAc)_2$ with macrocycles **24** (R = H or Me) at room temperature in TFE solution, and their structures were initially confirmed by HRMS and XRD analysis. Careful analysis of solid-state molecular structure indicated that Co(II) complexes **27** possess two acetates coordinated in a bidentate fashion. Notably, tridentate macrocycles **24** act as bidentate ligands, coordinated only through the pyridine and one amine. Upon increasing the temperature, the desired C-H activated cobalt(III) complexes **28** were obtained. Due to the stability of obtained Co(III)-aryl complexes **28**, they were successfully characterized by NMR and HRMS, providing spectra consistent with a Co(III) low spin diamagnetic metal center. Additionally, the authors explored the reactivity of isolated Co(III)-aryl compounds **28** in stoichiometric reactions with terminal and internal alkynes. Employing internal alkynes, the expected six-membered 1,2-dihydroisoquinolines **26** could be obtained in yields up to 72%, whereas terminal alkynes led to the formation of dihydroisoindoline **25** (5-membered ring) as a thermodynamically more stable product. It was observed that decreasing the reaction temperature or changing the electronic effects in alkynes, e.g., using phenylacetylene instead of 4-nitrophenylacetylene, led to the formation of a kinetic product (six-membered ring). In addition, using isolated Co(III) intermediates **28**, annulation reactions were also studied in a catalytic fashion. As a result, the desired products were obtained in very good yields, indicating that Co(III)-aryl complexes **28** are the reaction intermediates.



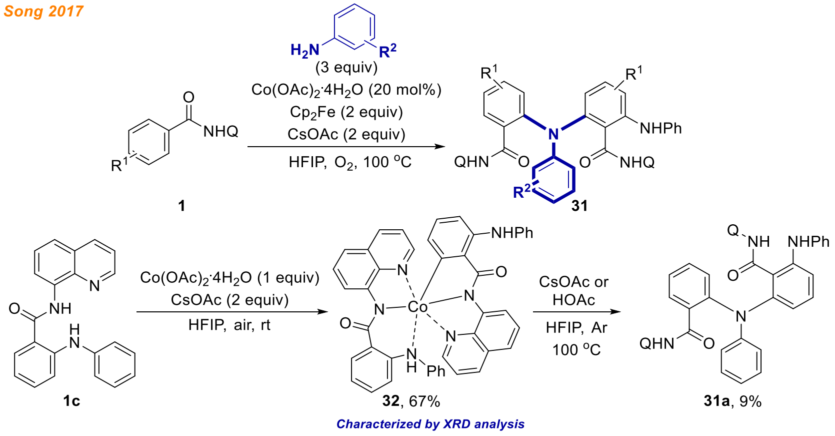
Scheme 10. Cobalt-catalyzed alkyne annulation and synthesis of Co(III)-aryl complexes **28** [31].

One year later, in 2017, Ribas group explored the formation of Aryl-Co(III) masked carbenes in cobalt-catalyzed C-H bond functionalization with diazo esters as a continuation of their previous work (Scheme 11) [32]. Optimization studies revealed that the developed protocol requires $Co(OAc)_2$ catalyst and H_2O as an additive to afford the desired isoquinoline **29** via annulation reaction with ethyl diazoacetate (EDA). The authors utilized previously isolated cobalt complex **28a** as the substrate and performed detailed mechanistic investigation under anhydrous reaction conditions. When **28a** reacted with ethyl diazoacetate, a single peak was observed by HRMS analysis. Authors proposed the formation of a putative aryl-Co(III)-carbene intermediate. Although attempts to unravel its nature by crystallographic analysis were unsuccessful, suitable crystals for XRD analysis were obtained by replacement of acetate anion in **28a** with *p*-substituted benzoates. This anion exchange facilitated a rapid color switch from red to orange in the reaction with EDA, and recrystallization from $CHCl_3$/pentane afforded orange crystals of Co(III) complex **30**. Similar to a previous report [31], isolated cobalt intermediates **28a** and **30** were used as catalysts, providing the desired product **29** with yields 67–87%, indicating that organometallic complexes **28a** and **30** are catalytically active species. Ribas and co-workers are continuing the investigation of Co(III)-aryl complex **28** reactivity towards other transformations [33].



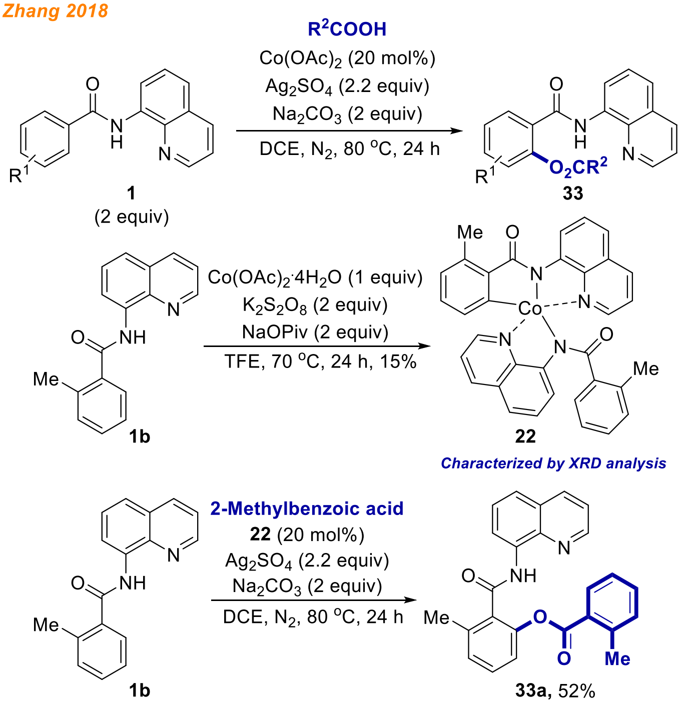
Scheme 11. Cobalt-catalyzed C-H bond functionalization with ethyl diazoacetate [32].

In the same year, Song and co-workers reported a selective and facile access to triarylamines **31** via cobalt-catalyzed oxidative C-H/N-H cross-coupling reaction (Scheme 12) [34]. During optimization of reaction conditions, authors were able to push the selectivity towards the desired product **31** over the dimerization side reaction of benzamides **1**. The best results were achieved, using optimized catalytic system, which consisted of $Co(OAc)_2 \cdot 4H_2O$ catalyst, ferrocene cooxidant and CsOAc in HFIP at 100 °C temperature under aerobic conditions. Furthermore, Co(III) complex **32** was obtained from the reaction of benzamide **1c** with stoichiometric amount of $Co(OAc)_2 \cdot 4H_2O$ at room temperature under air. Pleasingly, its structure was confirmed by XRD analysis. The authors demonstrated that cobaltacycle **32** under basic or acidic conditions delivered the triarylamine product **31a** only in 9% yield. Although other mechanistic experiments suggest a Co(II)-Co(III)-Co(I) catalytic cycle, based on the low yield of product **31a** formation from Co(III) complex **32**, the involvement of Co(IV) catalytic species cannot be excluded.



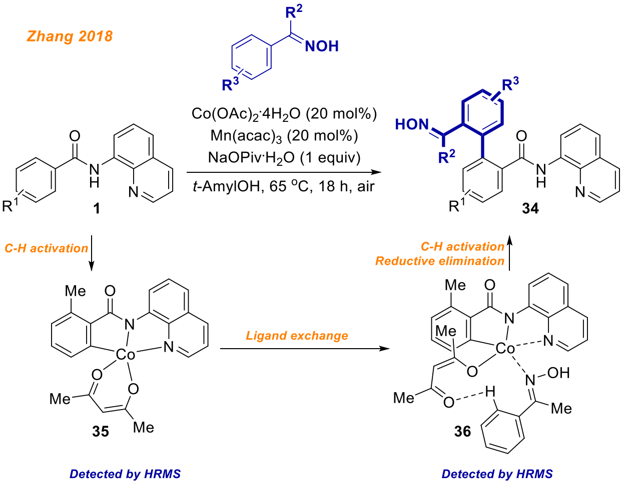
Scheme 12. Cobalt-catalyzed synthesis of triarylamines **31** [34].

In 2018, Zhang and co-workers reported a facile and powerful protocol for the cobalt-catalyzed C-H bond acyloxylation of benzamides **1** (Scheme 13) [35]. In the developed methodology anhydrous $Co(OAc)_2$ in combination with Ag_2SO_4 and Na_2CO_3 in DCE was found to be the catalytic system of choice. The optimized reaction conditions were compatible with a diverse substrate scope, delivering a broad variety of *o*-substituted benzamides **33** (44 products) with yields up to 99%. Additionally, radical-trapping and deuterium-labeling experiments were performed to understand the reaction mechanism in detail. Besides, authors synthesized Co(III)-aryl complex **22** based on a procedure previously described by Maiti and co-workers in 2016 [30], starting from methylbenzamide **1b**, and confirmed its structure by single-crystal X-ray diffraction analysis. Authors suggested that Co(III) complex **22** could be the key intermediate in this reaction as it catalyzed the model reaction, delivering product **33a** in 52% yield.



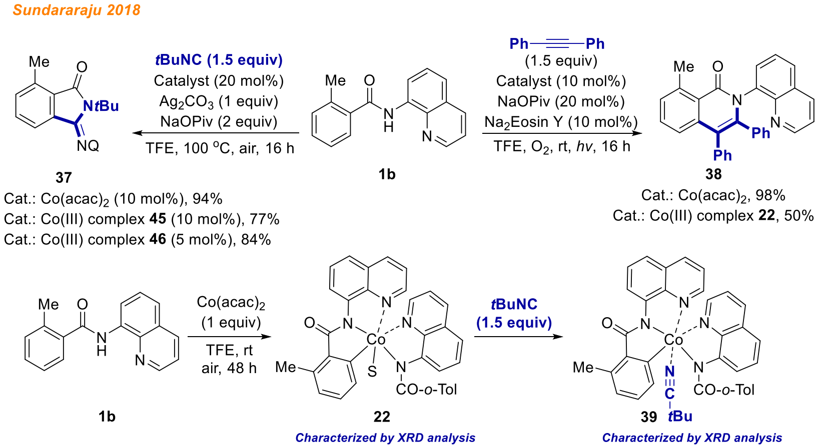
Scheme 13. Cobalt-catalyzed acyloxylation of benzamides **1** [35].

In the same year, the Zhang group reported a novel strategy for the synthesis of difunctional biaryls **34** from readily available benzamides **1** and oximes (Scheme 14) [36]. In contrast to the majority of cobalt-catalyzed benzamide **1** C-H bond functionalization reactions, the reported protocol is very mild as this transformation takes place at 65 °C temperature under air. The reported methodology demonstrates broad substrate scope as well as remarkable chemoselectivity towards cross-coupling. To gain insight into the reaction mechanism, the authors performed an intermolecular competition experiment of electronically differentiated benzamides as well as KIE experiments. In addition, both, C-H activated Co(III)-aryl complex **35** and oxime-coordinated Co(III)-aryl complex **36** were successfully detected by HRMS. Mechanistic studies along with detected Co(III) intermediates helped authors to propose the reaction mechanism, which is in accordance with the general Co(II)-Co(III)-Co(I) mechanism.



Scheme 14. Cobalt-catalyzed synthesis of biaryls **34** via C-H bond activation [36].

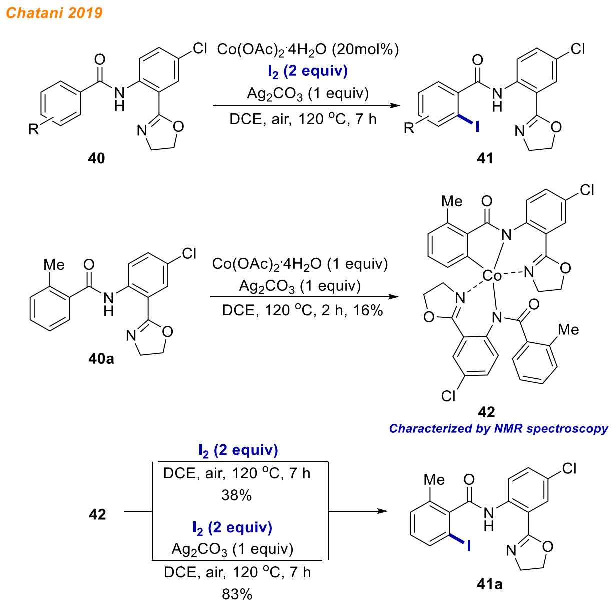
In 2018, the Sundararaju group developed a novel pathway for isonitrile insertion/acyl group migration between N-H and C-H bonds of benzamides **1b** through intramolecular *trans*-amidation catalyzed by Co(acac)$_2$ (Scheme 15) [37]. The authors demonstrated broad substrate scope yielding a wide variety of iminoisoindolinone derivatives **37** (42 products, yields up to 94%). Besides, significant mechanistic studies were performed, including KIE, H/D exchange, and radical trapping experiments. Moreover, the stoichiometric reaction of benzamide **1b** with Co(acac)$_2$ yielded C-H activated Co(III)-aryl complex **22**, which was previously described by Maiti [30], as well as later by the Zhang group [35]. The reaction of Co(III)-aryl complex **22** with *tert*-butyl isocyanide at room temperature in 10 min yielded Co(III) intermediate **39**, which was isolated and its structure was confirmed by HRMS and XRD analysis. Both intermediates **22** and **39** were used as catalysts for the transformation of benzamide **1b** to iminoisoindolinone derivative **37** under standard reaction conditions and were found to be active in catalysis.



Scheme 15. Cobalt-catalyzed C-H bond functionalization of benzamide **1b** [37,38].

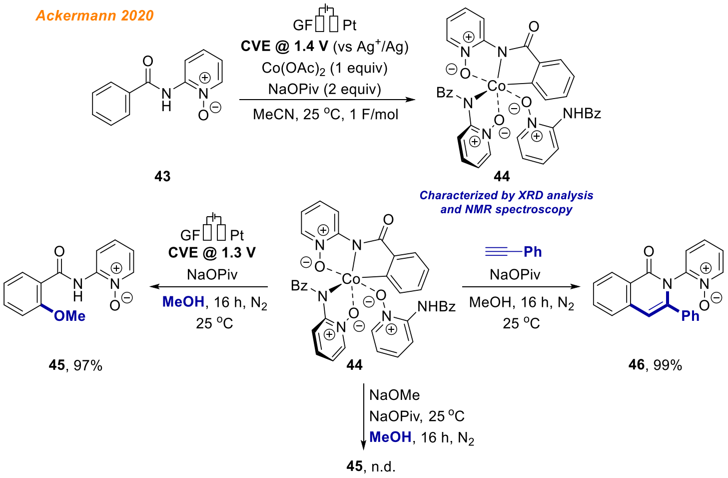
Later the same year, Sundararaju and colleagues reported a strategy for benzamide **1b** C-H and N-H bond annulation with alkynes by merging cobalt-mediated catalysis with photocatalysis (Scheme 15) [38]. Employing relatively similar reaction conditions to the group's previous report [35] and Na_2Eosin Y as the photoredox catalyst, various electron-donating and electron-withdrawing benzamides delivered isoquinolones with yields up to 99%. In addition, Co(III) complex **22** was found to be catalytically active in reaction with benzamide **1b**, delivering isoquinolone **38** with 50% yield in contrast to $Co(acac)_2$, which furnished the desired product with 98% yield.

A year later, in 2019, Chatani reported an efficient protocol for cobalt-catalyzed C-H bond iodination of benzamides **40** with elemental iodine (Scheme 16) [39]. Thus, 2-Aminophenyloxazoline-based bidentate chelation as a directing group in combination with $Co(OAc)_2{\cdot}4H_2O$ catalyst and Ag_2CO_3 oxidant were found to represent the optimal catalytic system for the synthesis of 2-iodobenzamides **41** in moderate to great yields. When methylbenzamide **40a** was treated with equimolar amount of $Co(OAc)_2{\cdot}4H_2O$ and Ag_2CO_3 in DCE at 120 °C for 2 h, the Co(III) complex **42** was successfully isolated and characterized by HRMS and NMR spectroscopy. Interestingly, without the oxidant Co(III), complex **42** furnished the iodination product only in 38% yield along with a significant amount of unidentified byproducts, whereas in the presence of Ag_2CO_3 the yield increased to 83%, and no byproducts were detected. Based on these experiments, the authors concluded that despite the catalytic activity of Co(III) complex **42**, silver oxidant is an essential component of the reaction, promoting the iodination reaction and eliminating the formation of byproducts. The authors therefore speculated that Co(III) complex **42** is not the key intermediate of the reaction, but exists as a resting state.



Scheme 16. Cobalt-catalyzed iodination of benzamides **40** with molecular iodine [39].

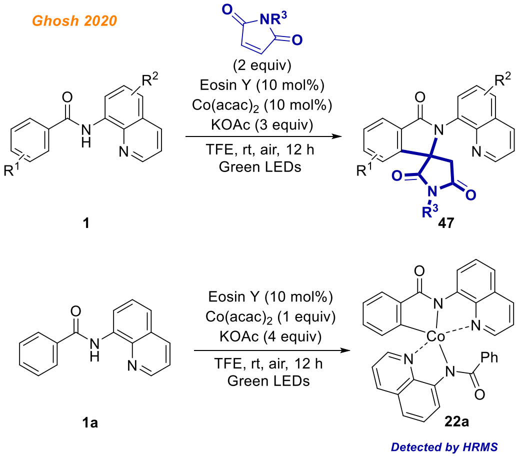
In 2020, the Ackermann group identified and characterized electrochemically generated high valent cobalt (III/IV) complexes as crucial intermediates in electrochemical cobalt-catalyzed C-H bond functionalization reactions (Scheme 17) [40].



Scheme 17. Electrochemical synthesis of Co(III)-aryl complex 44 and its reactivity studies [40].

The envisioned 18e$^-$ cobaltacycle **44** was electrochemically synthesized starting from benzamide **43** and an equimolar amount of Co(OAc)$_2$, and its structure was unambiguously confirmed by NMR spectroscopy, ESI-MS, and XRD analysis. Investigating the red-ox potential by means of voltammetry, the authors were able to affirm the anodic generation of Co(IV) complexes. Interestingly, the authors observed the formation of alkoxylated product **45** from Co(III)-aryl complex **44** only when voltage was applied. Such a result supports the oxidation-induced reductive elimination pathway involving Co(IV) species. At the same time, Co(III) complex **44** reaction with phenylacetylene proceeded smoothly, allowing to obtain product **46** in 99% yield. These findings are indicative of different mechanisms being operative for the C-O versus C-H formations.

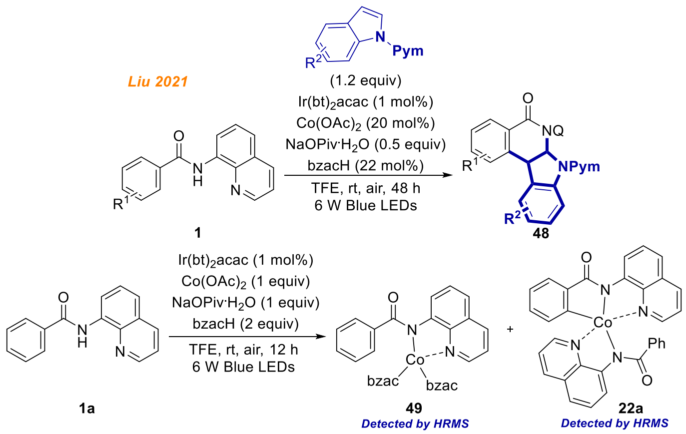
A novel methodology merging visible-light photocatalysis and cobalt catalysis was reported by the Ghosh group in 2020 (Scheme 18) [41].



Scheme 18. Synthesis of isoindolone spirosuccinimides **47** by merging photocatalysis and cobalt-catalyzed C-H bond activation [41].

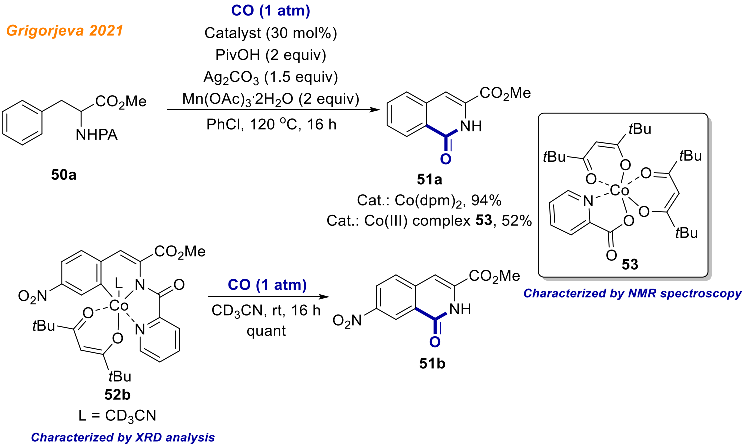
The developed protocol gives an efficient access to isoindolone spirosuccinimides **47** by the oxidative cyclization of benzamides **1** with maleimides. The main advantage of the developed transformation was the use of photocatalyst Eosin Y, a commonly available organic dye, instead of sacrificial metal oxidant to reoxidize the in-situ formed low-valent Co(I) to active high valent Co(II)/Co(III) species to continue the catalytic cycle. Mild reaction conditions tolerated well a broad variety of benzamides **1** containing substituents both in phenyl moiety and in the aminoquinoline directing group moiety, delivering isoindolones **47** with yields up to 92%. It should be noted that authors were able to identify a five-membered Co(III)intermediate **22a** by HRMS, which validated the involvement of Co(III) complex **22a** in the reaction mechanism, although no further identification of reaction intermediates was performed.

One year later, in 2021, Liu and co-workers depicted metallaphotoredox dearomatization of indoles for the facile generation of indoloisoquinolinones **48** via [4 + 2] annulation reaction with benzamides **1** (Scheme 19) [42]. The developed catalytic system employed $Co(OAc)_2$ catalyst and $Ir(bt)_2acac$ photocatalyst, sodium pivalate additive, and benzoylacetone ligand in TFE at room temperature. Similar to Ghosh's report [41], no external oxidant was required due to photocatalytic reoxidation of the catalyst. The substrate scope studies showed that both electron-rich and electron-poor substrates displayed similar reactivity and gave the products mostly in good to excellent yield (up to 92%). Control experiments revealed the involvement of single electron transfer processes, as with the addition of radical scavengers, the generation of product was entirely suppressed. To gain insight into the mechanism, the authors performed deuterium-labeling experiments, as well as studied KIE of the reaction. In addition, the authors synthesized $Co(bzac)_3$, which was found to be catalytically competent. Moreover, two Co(III) complexes **49** and **22a** were detected by ESI-HRMS, establishing the intermediacy of the related Co(III) system in the present reaction.



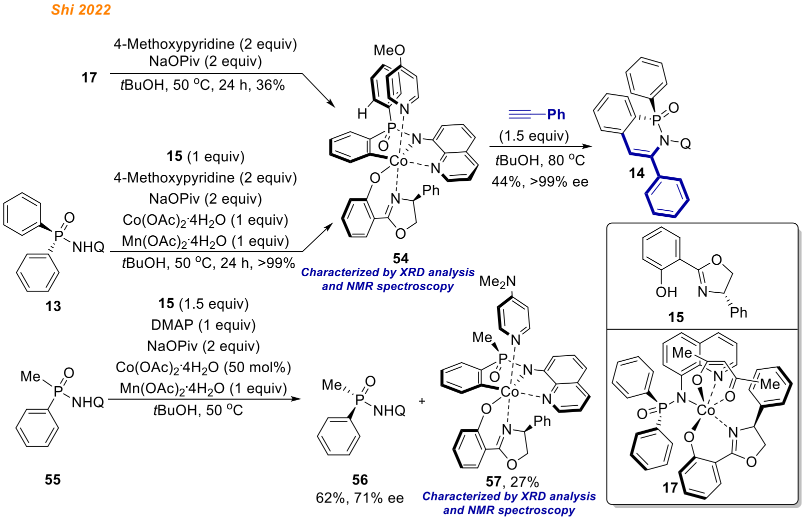
Scheme 19. Synthesis of indoloisoquinolinones **48** via metallaphotoredox catalysis [42].

In the same year, Grigorjeva and co-workers reported an efficient methodology for the synthesis of dihydroisoquinolinolones **51** via cobalt catalyzed C-H bond carbonylation of phenylalanine derivatives **50** (Scheme 20) [43]. Interestingly, in this transformation, the picolinamide directing group revealed its traceless nature as it was cleaved in situ under the reaction conditions. The authors were able to demonstrate a diverse substrate scope, delivering the desired *N*-unsubstituted cyclization products **51** with moderate to excellent yields (up to 95%). Furthermore, it was shown that the developed methodology may be applicable to a late-stage functionalization of short peptides, although partial racemization of some products was observed. Besides, under the standard reaction conditions, authors were able to isolate the key intermediates, including Co(III) complex **53**. The employment of Co(III) intermediate **53** as the reaction catalyst gave product **51a** in 52% yield. In addition, C-H activated Co(III)-aryl intermediate **52b** was successfully isolated, and its structure was unambiguously confirmed by XRD analysis. Pleasingly, under CO (1 atm) at room temperature, cobaltacycle **52b** quantitatively formed C-H carbonylation product **51b**, which supported the author's conclusion this complex most likely was the key intermediate of the reaction.



Scheme 20. Cobalt-catalyzed carbonylation of phenylalanine derivatives **50** [43].

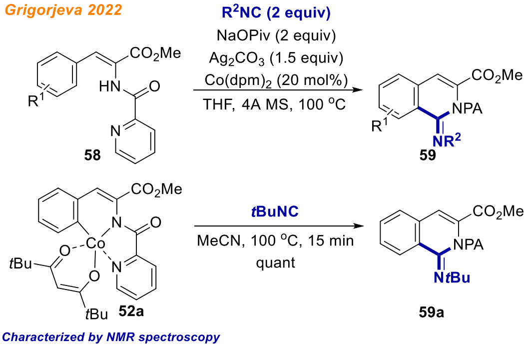
In 2022, along with cobalt complexes formed in ligand exchange/oxidation step, the Shi group were able to synthesize and isolate C-H activated Co(III)-aryl intermediates (Scheme 21) [28]. For example, the reaction of previously isolated Co(III) complex **17** was conducted in the presence of NaOPiv and 4-methoxypyridine as a neutral ligand to stabilize the resulting cobalt complex. As a result, Co(III)-aryl complex **54** was obtained in 36% yield as a single octahedral diastereomer via asymmetric C-H activation step.



Scheme 21. Synthesis of Co(III)-aryl intermediate **54** [28].

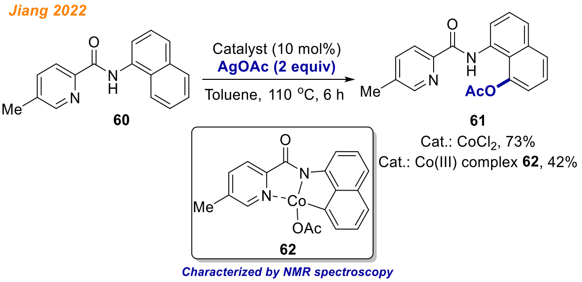
Alternatively, cobalt(III) intermediate **54** was also obtained in quantitative yield directly from phosphinic amide **13** by the reaction with equimolar amount of ligand **15**, Co(II) acetate, oxidant, NaOPiv, and 4-methoxypyridine as a stabilizing ligand. Notably, the configuration of azaphosphinine oxide **14** matches the stereochemistry of phosphorus center in **17**, which led authors to consider enantio-determining C-H bond cleavage. Regarding this, authors performed stoichiometric kinetic resolution of racemic **55**. It was revealed that only one enantiomer gave corresponding Co(III) intermediate **57**, which further suggested that the chirality of the phosphorus center was established through enantio-determining C-H bond cleavage.

As a continuation of their previous work on amino acid C-H functionalization, in 2022, Grigorjeva and co-workers reported novel protocol for the cobalt-catalyzed C-H bond imination of α,β-unsaturated phenylalanine derivatives **58** using isocyanides (Scheme 22) [44]. The substrate scope was explored using several α,β-unsaturated phenylalanines **58** and different isocyanides, delivering 26 different iminoisoquinolines **59** in good to excellent yields (up to 96%). Although picolinamide did not act as a traceless directing group, as shown in their previous report [43], it can be easily cleaved under the reductive conditions using $LiAlH_4$ or Zn/AcOH. In addition, the developed methodology was applied for the synthesis of PDE5 inhibitor. In order to gain insight into the reaction mechanism, the authors performed series of control experiments, including ligand exchange and competition experiments, H/D scrambling and KIE studies. Besides, a stoichiometric experiment with Co(III)-aryl complex **52a** was performed. Interestingly, **52a** in the reaction with *tert*-butyl isocyanide gave product **59a** in quantitative NMR yield in the absence of external oxidant, indicating that **59a** is very likely the intermediate of proposed catalytic cycle.



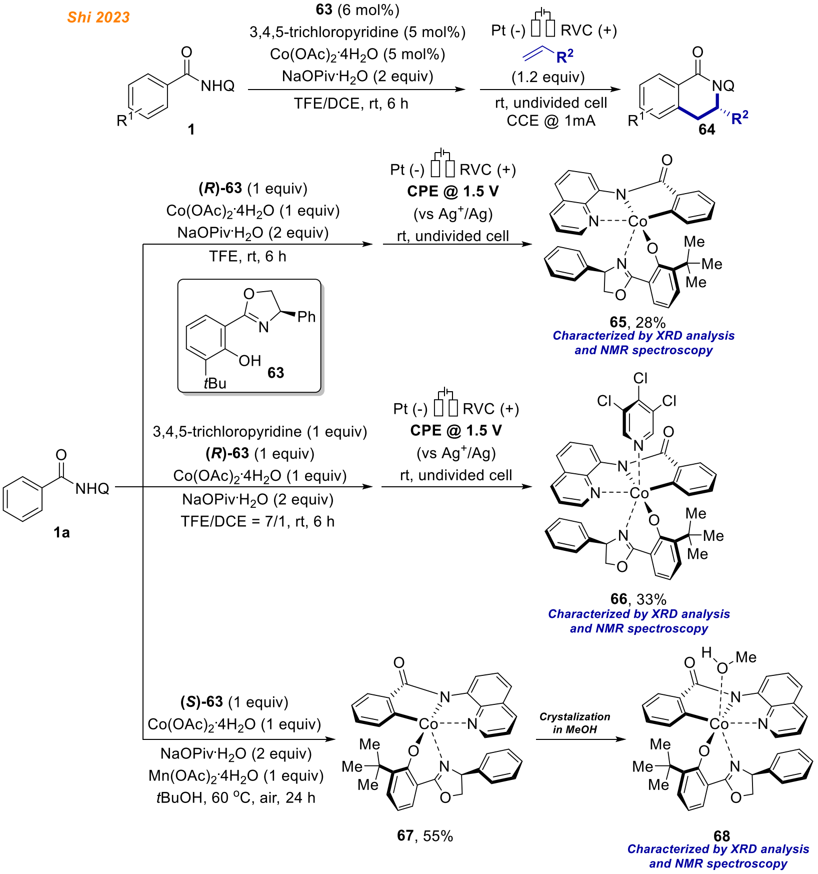
Scheme 22. Cobalt-catalyzed imination of phenylalanine derivatives **58** [44].

In the same year, Jiang and colleagues demonstrated an interesting approach towards C-H bond acyloxylation of picolinamides **60** with silver carboxylates under cobalt catalysis (Scheme 23) [45]. Generally, substituted silver carboxylates and substituted picolinamides **60** were reactive, delivering a very wide and diverse product scope consisting of 73 different products with good to excellent yields (up to 94%). Investigation of the reaction mechanism by means of KIE studies led to the conclusion that C-H bond activation may not be the turnover-limiting step. Furthermore, authors were able to obtain chelated Co(III)-aryl complex **62**, which was accurately characterized by NMR and HRMS analyses. The employment of Co(III) intermediate **62** as the reaction catalyst gave the desired product **61** in 42% yield, whereas under standard reaction conditions using $CoCl_2$ catalyst, it was obtained in 73% yield. From these results, the authors concluded that complex **62** was the key intermediate in the developed C-H bond acyloxylation reaction.



Scheme 23. Cobalt-catalyzed acetoxylation of picolinamide **60** [45].

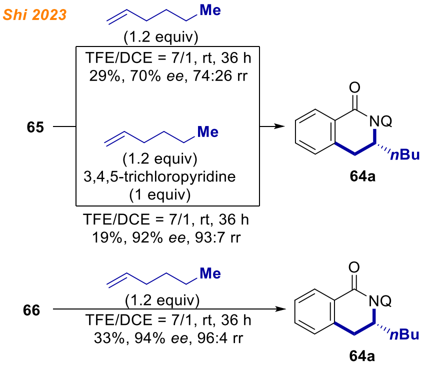
Very recently, an enantio- and regioselective electrooxidative cobalt-catalyzed C-H/N-H annulation reaction with alkenes was developed by Shi and co-workers (Scheme 24) [46]. In their report, π–π interactions between the phenyl ring in the oxazoline ligand **63** and the quinoline moiety of the benzamides **1** secured the chirality at cobalt, leaving chiral cave in one direction open for alkene coordination, facilitating the formation of annulation products **64** in high enantio- and regioselectivities (up to 99% *ee*).



Scheme 24. Synthesis of Co(III)-aryl complexes **65–68** [46].

Additionally, octahedral Co(III) complexes were synthesized and characterized to understand the coordination fashion of cobalt catalyst and the mode of stereoinduction. Benzamide **1a** in the reaction with an equimolar amount of $Co(OAc)_2 \cdot 4H_2O$ and oxazoline ligand (*R*)-**63** under electrolysis conditions provided *penta*-coordinated Co(III)-aryl complex **65** in 28% yield. The addition of 3,4,5-trichloropyridine as a coordinative ligand under similar reaction conditions provided *hexa*-coordinated Co(III)-aryl complex **66** in 33% yield. The authors note that both **65** and **66** were stable at ambient temperature and were fully characterized by NMR and ESI-MS analyses. However, attempts to obtain single-crystals for X-ray diffraction analysis were unsuccessful. On the other hand, under thermal conditions, using oxazoline ligand (*S*)-**63** analogous *penta*-coordinated Co(III)-aryl, complex **67** was obtained in 55% yield. Complex **67** crystallization from MeOH gave Co(III) complex **68**, whose structure was unambiguously confirmed by XRD analysis.

Interestingly, the stoichiometric reaction of Co(III)-aryl complex **65** with hex-1-ene yielded product **64a** with moderate enantioselectivity and poor regioselectivity, which was attributed to the lack of secondary bond interaction (Scheme 25) [46]. The authors found, that enantio- and regioselectivities reappeared with the addition of 1 equivalent of 3,4,5-trichloropyridine, which acted as a coordinative ligand. Moreover, *hexa*-coordinated Co(III)-aryl complex **66** gave product **64a** with excellent enantioselectivity and regioselectivity. These results led authors to conclusion that the combination of oxazoline and pyridine ligands is essential to ensure high enantio- and regio- selectivity for the developed methodology.

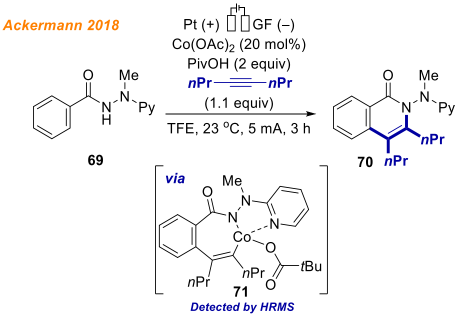


Scheme 25. Stoichiometric reactions of Co(III)-aryl complexes **65** and **66** with hex-1-ene [46].

5. C-H Bond Functionalization

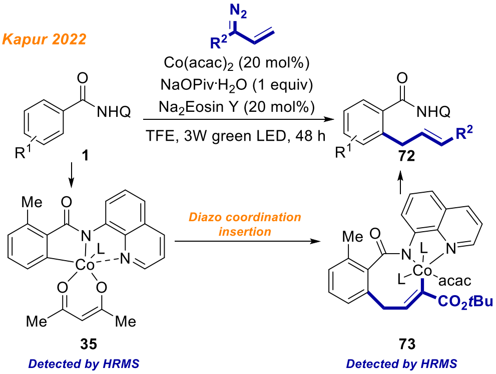
The C-H bond functionalization is the third elementary step in the generally accepted high-valent cobalt catalysis mechanism occurring after C-H bond cobaltation. As we described above, the plausible intermediacy of C-H activated Co(III)-aryl complexes has been evidenced by numerous groups by successfully exploiting such isolated or synthesized complexes as catalysts or substrates in stoichiometric amounts to obtain C-H bond functionalization products. However, the detection and/or isolation of potential cobalt intermediates, which are operative after the C-H bond metalation step, is a challenging task due to the reactivity of such cobalt complexes. As we described before, in 2018, Sundararaju and co-workers reported *tert*-butyl isocyanide coordinated cobalt complex **39**, which formed after Co(III)-aryl complex **22** reaction with *tert*-butyl isocyanide at room temperature (Please see Scheme 15). Although the complex was isolated and its structure was confirmed by HRMS and XRD analyses, the authors was not able to detect further reaction intermediates [38]. As far as we know, only two examples can be found in the literature describing Co(III) complexes formed after migratory insertion process.

In 2018, Ackermann's group reported the cobalt-catalyzed electro-oxidative C-H/N-H activation of benzamides **69** with internal alkynes (Scheme 26) [47]. In their study, the catalytic system employed a Co(OAc)$_2$ catalyst, PivOH additive, and electricity as the sole oxidant in TFE at room temperature to deliver isoquinolinones **70** in moderate to great yields (up to 96%). Additionally, the authors were able to detect by ESI-HRMS Co(III) intermediate **71**, which formed after the migratory insertion of alkyne into the Co-Ar bond. Moreover, computational mechanistic studies provided further support for the formation of the observed seven-membered Co(III) species **71**, which after reductive elimination delivered the desired product **70** and Co(I).



Scheme 26. Cobalt-catalyzed electrooxidative benzamide **69** reaction with alkyne [47].

Kapur and co-workers, in late 2022, reported an interesting approach towards benzamide **1** C-H bond allylation using merged cobalt and photoredox catalysis (Scheme 27) [48]. In contrast to Maiti's allylation with terminal alkenes [26,30], authors used vinyldiazo esters as allylating reagents. As a result, allylbenzamides **72** were obtained in moderate yield, although the developed methodology proved to be effective for the late-stage diversification of biologically active molecules, including cholesterol, nerol, and others. In the proposed reaction mechanism, after ligand exchange and C-H activation, cobalt intermediate **35** could form. The authors propose, that Co(III)-aryl complex **35** undergoes a diazo coordination and insertion, which leads to the formation of the Co(III) intermediate **73**. Both cobaltacycles **35** and **73** were observed by HRMS, although none of them was isolated from the reaction.

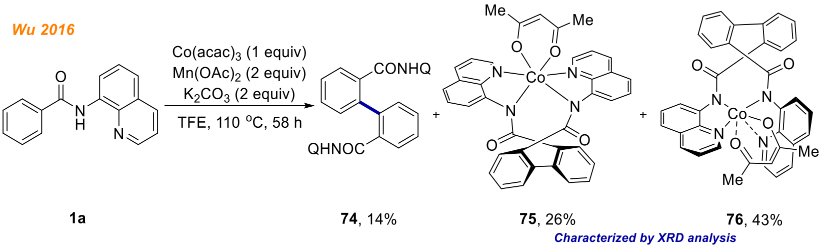


Scheme 27. Benzamide **1** C-H bond allylation using merged cobalt and photoredox catalysis [48].

6. Oxidation

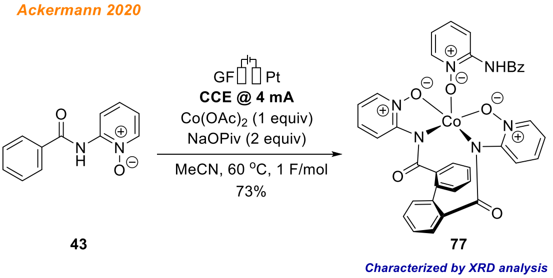
The last elementary step of C-H bond functionalization reactions is re-oxidation of the cobalt catalyst after reductive elimination to return the active Co(III) species to the catalytic cycle. Although no Co(I) species are isolated, there have been few reports on plausible reaction intermediates arising after oxidation of Co(I) species. For example, Grigorjeva and colleagues were able to isolate Co(III) catalyst coordinated to picolinamide, which formed after the hydrolysis of the directing group (please see Scheme 20) [43].

In 2016, Wu and colleagues studied the cobalt-catalyzed homo-coupling of benzamide **1** derivatives (Scheme 28) [49]. Prior to optimization of the reaction conditions, Daugulis and co-worker reported their results on the same transformation, focusing their attention on different substrates for the dimerization reaction. Nevertheless, during initial studies, authors were able to isolate Co(III) complexes **75** and **76** in 26% and 43% yields, respectively. The difference between **75** and **76** is the orientation of the acetylacetone group attached to the cobalt center. In addition, XRD analysis was performed, unambiguously confirming structures to be biaryl-linked Co(III) complexes, which would lead to the desired product **74** after demetallation.



Scheme 28. Cobalt-catalyzed benzamide **1a** dimerization [49].

In 2020, along with Co(III) complexes which were formed in the C-H bond activation step, Ackermann and colleagues noticed the formation of a significant amount of byproducts, especially with the electron rich substrates **43** [40]. Based on their mechanistic studies, authors hypothesized a possible oxidation of Co(III)-aryl species to Co(IV) complexes, which would undergo oxidation-induced reductive elimination for homo-coupling of the coordinated substrates **43**, leading to paramagnetic Co(II) complexes. Further, various solvents were probed, and the reaction temperature was adjusted. As a result, benzamide **43** delivered the desired Co(II) complex **77**, using MeCN at 60 °C (Scheme 29). Moreover, the structure **77** was completely verified by XRD characterization, providing strong support for an oxidation-induced reductive elimination from a high-valent Co(IV) intermediate.



Scheme 29. Synthesis of paramagnetic Co(II) complex **77** from benzamide **43** [40].

7. Conclusions and Outlook

In this review, we have summarized the overall current progress on the isolation and identification of key cobalt intermediates in cobalt-catalyzed, bidentate-chelation assisted

C-H bond functionalization reactions. The general Co(II)-Co(III)-Co(I) mechanism, which is based on literature reports, is overviewed in detail according to the elementary steps.

The identification and characterization of reaction intermediates over the years has become an essential approach for understanding the reaction mechanism, which along with additional mechanistic experiments, including kinetic isotope effects, labeling studies, competitive experiments, and others, can serve as direct and indirect evidence to decipher the full picture of the catalytic cycle. The first two elementary steps of the C-H functionalization reaction, i.e., substrate coordination/oxidation and C-H bond activation, are relatively well-studied and supported by a diverse scope of isolated key Co(III) intermediates. Most of the isolated key intermediates are Co(III) 18 e- complexes. Typically, octahedral Co(III) 18 e- complexes are considered as stable and relatively inert species, which tend to vacate at least one coordination site to participate in the reaction. Based on this fact, the most likely key reaction intermediates are coordinatively unsaturated 16 e- or 14 e-complexes, which react with solvent or other ligand upon isolation and/or crystallization to form stable species.

However, the next elementary steps of the reaction mechanism (C-H bond functionalization and catalyst re-oxidation) are studied much less and are supported by only a few examples of isolated or detected cobalt species. Difficulties in isolating potential key intermediates after the C-H bond activation step may be attributed to the high reactivity of such cobalt species, which makes it challenging even to detect by HRMS analysis. First reports appeared only five years ago and currently only two examples of Co(III) species after the migratory insertion step are known. Therefore, this part of general catalytic cycle remains underdeveloped. The creation of novel methods for the isolation and/or characterization of such intermediates will very likely be an enormous breakthrough for the understanding of the mechanism of cobalt-catalyzed C-H functionalization reactions and represent a valuable direction for future research.

Although many research groups have succeeded in the isolation of Co(III) key reaction intermediates, and the general Co(II)-Co(III)-Co(I) mechanism is studied in detail, currently, there is indisputable evidence for the Co(II)-Co(III)/Co(IV)-Co(II) catalytic cycle which could be operative depending on the used reaction component. Numerous examples of the cobalt-catalyzed C-H bond functionalization methodology that are not consistent with the Co(II)-Co(III)-Co(I) mechanism continue to be discovered. However, the Co(II)-Co(III)/Co(IV)-Co(II) pathway is not completely confirmed due to the lack of evidence and difficulties in obtaining it. From our perspective, this is another highly important future direction and a challenging task for researchers.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

acac = acetylacetone, bzac = benzoylacetone, CCE = constant current electrolysis, CPE = constant phase element, CVE = constant voltage electrolysis, Cp* = pentamethylcyclopentadienyl-, dpm = dipivaloylmethane, EDA = ethyl diazoacetate, Ir(bt)$_2$acac = Bis(2-benzo[*b*]thiophen-2-ylpyridine)(acetylacetonate) iridium(III), PA = picolinamide, Q = 8-aminoquinoline.

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Diastereoselective C—H Functionalizations

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Key Points

- Diastereoselective C—H functionalization using first-row transition metal catalysis
- Diastereoselective C—H functionalization using second-row transition metal catalysis
- Diastereoselective C—H functionalization using third-row transition metal catalysis

List of Abbreviations

Acac acetylacetone
(R,R)-BDPP (2R,4R)-(+)-2,4-Bis(diphenylphosphino)pentane
Binap 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BINOL 1,1′-bi-2-naphthol
Box bisoxazoline
BPin pinacolborane
CDI 1,1′-carbonyldiimidazole
Coe cyclooctene
Cp* pentamethylcyclopentadienyl
Cy cyclohexyl
DG directing group
EDG electron donating group
FG functional group
Hex hexyl
HFIP 1,1,1,3,3,3-hexafluoroisopropanol
Ind* heptamethylindenyl
Meoc methyloxycarbonyl

NFSI N-fluorobenzenesulfonimide
Ns *p*-nitrobenzenesulfonyl
PhthN phthalimido
Pin pinacol
PMBS *p*-mercuribenzenesulfonate
PMP *p*-methoxyphenyl
pym pyrimidine
Q 8-aminoquinoline
t-amyl 2-methylbutan-2-ol
TBDPS *t*-Bu diphenylsilyl
TBME *t*-Bu methyl ether
TBS tert-butyldimethylsilyl
TFE 2,2,2—trifluoroethanol
TMPH 2,2,6,6-tetramethylpiperidine
Tol *p*-tolyl
TPCP tetraphenylcyclopentadienone
TRIS tris(hydroxymethyl)aminomethane

Abstract

Over the past two decades the transition metal-catalyzed C—H bond activation and functionalization has earned an enormous interest, and has recently emerged as an attractive and powerful tool for construction of a diverse variety of organic molecules due to its step- and atom-economic proficiency. In this chapter we will summarize the developed methodology using first, second and third-row transition metal catalysts toward diastereoselective C—H bond functionalization reactions.

Introduction

The main aim of organic synthetic chemistry is to construct more complex structures from simple molecules. Classical organic synthesis often relies on functional group manipulations—reaction sequence to obtain desired products. Direct functionalization of ubiquitous C—H bonds is challenging and often requires harsh conditions due to the low reactivity of C—H bonds. Transition metal-catalyzed C—H bond activation and functionalization has recently emerged as a powerful synthetic approach to transform relatively unreactive C(sp^2)-H and C(sp^3)-H bonds to other functional groups (Fig. 1). Nowadays transition metal-catalyzed C—H bond activation and functionalization strategy is an integral part of organic synthesis tools and shows continuous impact in the field of drug discovery, natural product synthesis, and material sciences.[1–7]

In this chapter, we will overview transition metal-catalyzed diastereoselective C—H bond functionalization reactions. The examples are organized based on the transition metal used for the transformation. Herein we place the greatest emphasis on first-row transition metal catalysis, which recently has earned enormous interest, but lacks the general review articles highlighting and covering developments for the diastereoselective C—H functionalizations.

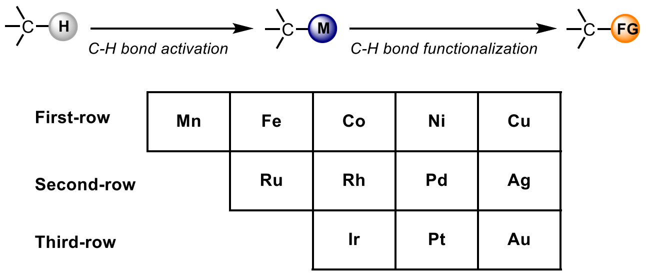
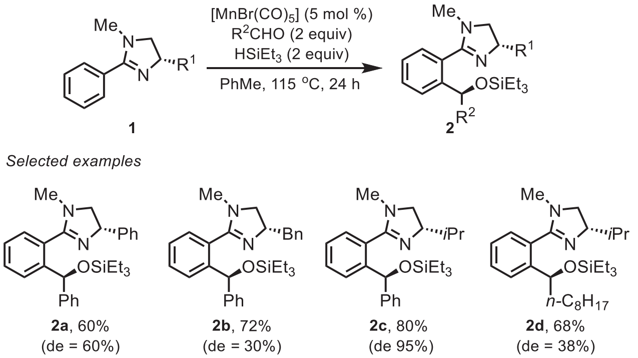


Fig. 1 Transition metals and C—H bond functionalization reaction.



Scheme 1 Manganese-catalyzed phenylimidazoline **1** C—H functionalization.

Diastereoselective C—H Bond Functionalization

First-Row Transition Metals

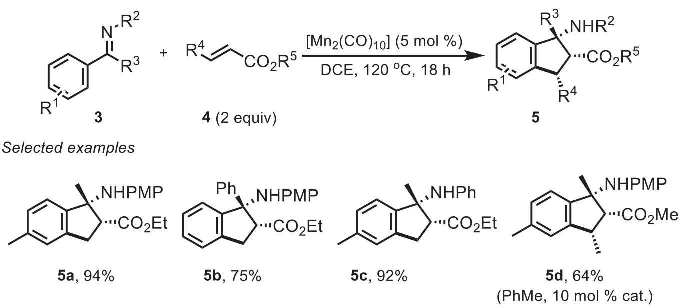
Significant progress in C—H bond functionalization methodology development has been made using second-row transition metals. However, the past decade has revealed the use of first-row transition metal catalysts for C—H bond functionalization as an attractive alternative to the traditional precious metal catalysts for their unique reactivity, low cost and environmentally friendly properties.[8–10] In this section we will highlight the important examples on diastereoselective C—H bond functionalization using first-row metal catalysts.

Manganese

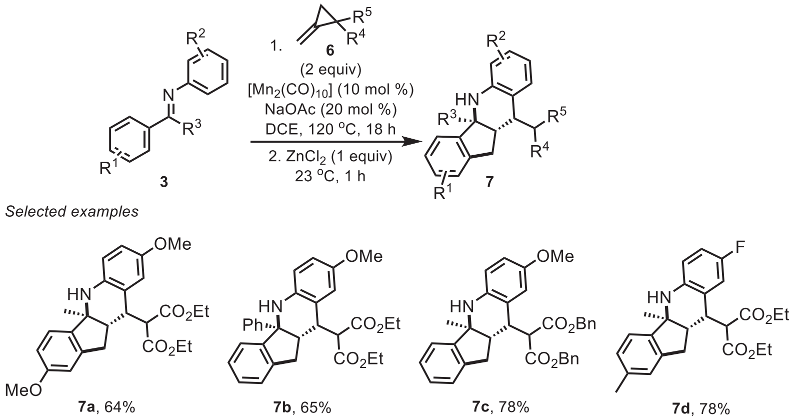
Manganese is the 12th most abundant element in the Earth's crust and the third most abundant transition metal (after iron and titanium).[11] Due to the low cost and low toxicity, it is considered as particularly attractive alternative to noble transition metal catalysts, however manganese(I) catalyzed organometallic C—H bond activation and functionalization only recently appeared as an increasingly viable tool in organic synthesis.[11–13]

Pioneering progress in Mn(I)-catalyzed C—H bond functionalization was made by Kuninobu, Takai and coworkers in 2007, when diastereoselective insertion of aldehydes into a C(sp^2)-H bond of aromatic compounds **1** was demonstrated.[14] The reported protocol employed [MnBr(CO)$_5$] catalyst in combination with corresponding aldehyde and triethylsilane to yield silyl enol ethers **2** in good yields and moderate diastereoselectivity (Scheme 1). In reported protocol, chiral imidazolines were used as the directing groups. Interestingly, in imidazoline **1c** (bearing an isopropyl group at the stereogenic center) reaction with benzaldehyde, the corresponding silyl ether **2c** was obtained in higher yield (80%) and greater diastereomeric excess (*de* 95%) than other products. Using alkyl aldehyde for the reaction, the diastereomeric excess of silyl ether **2d** somewhat decreased to 38%. Unfortunately, the developed method for diastereoselective transformation was limited to only 4 substrates.

Imine **3** reactions with α,β-unsaturated esters **4** employing [Mn$_2$(CO)$_{10}$] catalyst were demonstrated by Ackermann and coworkers in 2015 (Scheme 2).[15] The resulting products were β-amino acid esters **5** with unusual *cis* configuration. Conditions were considerably milder if compared to similar reaction using rhenium complex, besides additional amines or metal acetates



Scheme 2 Manganese-catalyzed annulation between imines **3** and alkenes **4**.



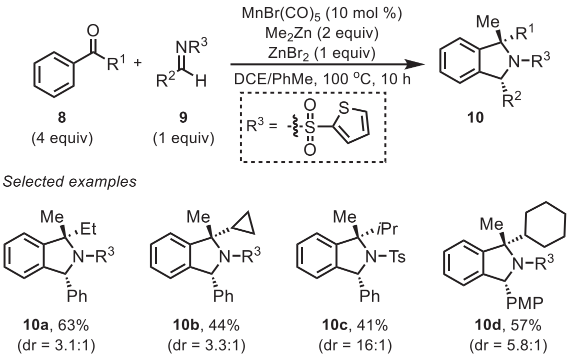
Scheme 3 Manganese-catalyzed tetracycle **7** formation from imines **3** and methylcyclopropanes **6**.

were not required for an efficient alkene annulation process. Substrate scope demonstrated reactions with different *N*-protecting groups, esters and substituents in the dihydroindene ring. Furthermore, reaction was not limited to terminal alkenes, since *E*-isomers were competent substrates, whereas alkene *Z*-isomers gave only traces of desired product. Moreover, β-aminoester **5d** was obtained with excellent control of all three contiguous stereogenic centers. From mechanism studies it was suggested that the chelation of the imino group and the ester enolate by the manganese ion facilitates cyclization which leads to exclusive *cis* diastereoselectivity.

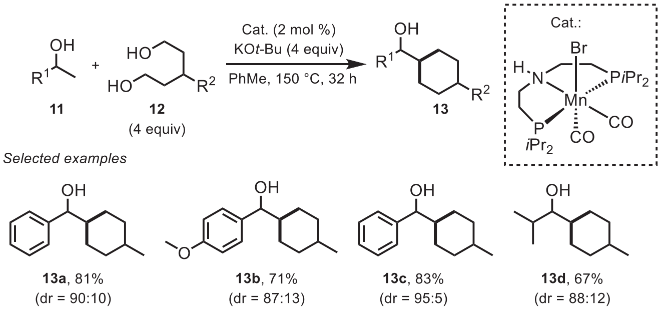
The reactivity of imines **3** toward Mn(I)-catalyzed C—H functionalization was further explored by Ackermann and coworkers in 2017.[16] They reported a novel method for the synthesis of polycyclic anilines **7** through a cascade C—H activation/Povarov manifold *via* manganese-catalyzed imine **3** reactions with methylenecyclopropanes **6** (Scheme 3). Pleasingly, all tetracyclic products **7** were obtained with excellent diastereoselectivity as single isomers. While only ester functionalities were shown as the substituents on the methylenecyclopropane, diverse substitution patterns in the imine component ring delivered the desired products in generally very good yields. Moreover, even imine **3d** featuring electron-deficient *N*-aryl ring, was compatible substrate under the reaction conditions and yielded tetracycle **7d** as a single diastereomer in 78% yield.

In the same year, Wang and coworkers depicted novel methodology for manganese catalyzed synthesis of isoindolines **10** (Scheme 4).[17] During the optimization studies, authors found that the three-component reaction of ketone **8**, imine **9** and dimethylzinc could be achieved at elevated temperature with two equivalents of Me_2Zn, yielding isoindolines **10** with moderate to good yields and diastereoselectivity. Additionally, two different products were selected for X-ray diffraction analysis, with which the major *cis*-diastereomer formation was unambiguously confirmed.

In 2019 Leitner and coworkers reported a manganese-catalyzed reaction between diols **12** and secondary alcohols **11** for the diastereoselective synthesis of cycloalkanes **13** (Scheme 5).[18] Various aromatic and aliphatic secondary alcohols **11** were coupled



Scheme 4 Manganese-catalyzed isoindoline **10** synthesis.



Scheme 5 Manganese-catalyzed reaction between diols **11** and secondary alcohols **12**.

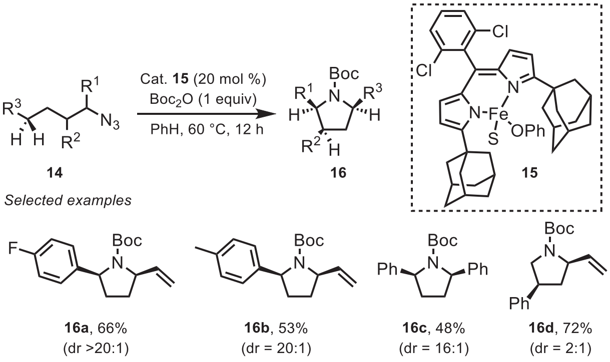
with several substituted 1,5-pentanediols **12** to generate substituted cyclohexanes **13** with very good to high yields and moderate to high diastereoselectivity. It is worth to mention, that the developed methodology allowed the construction of cycloheptane and cyclopentane derivatives by variation of the carbon chain in the diol component.

Iron

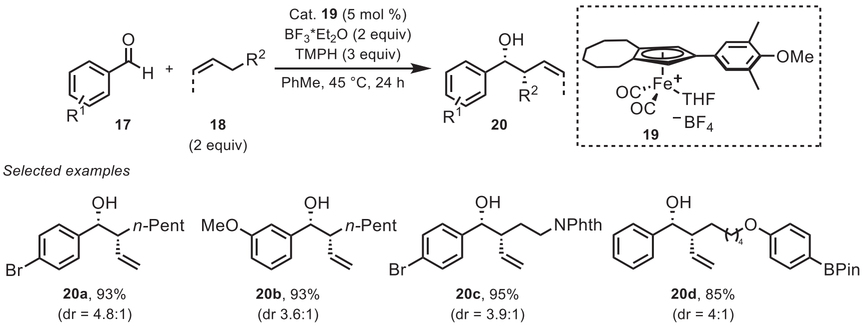
Iron is the most abundant transition metal in the Earth's crust. Such abundance accounts for low cost as well as low biological toxicity, therefore development of iron catalysis is desirable from the sustainability and economical points of view.[19–22] The application of iron catalysis for C—H bond activation and functionalization has been relatively recently developed and the first reported example dates back to 2008.[23] However, several examples on diastereoselective C—H bond functionalization in literature were found.

In 2017, Betley and coworkers reported a diastereoselective azide **14** C—H bond amination reaction using dipyrrinato-iron phenoxide complex **15** (S = THF) as the reaction catalyst (Scheme 6).[24] The reaction conditions were mild and provided 2,5-disubstituted pyrrolidines **16** with >20:1 *syn*:*anti* diastereoselectivity, although majority of substrates gave corresponding products with low to moderate yields (23—72%). The *syn* selectivity of the developed reaction was additionally proved by ^{1}D NOESY analysis of deprotected pyrrolidines and X-ray diffraction analysis using single crystals of the isolated iron adduct. Despite the great diastereoselectivity, the developed method was limited mostly to γ-substituted azides.

Quite recently, in 2023, Wang and coworkers introduced a new cationic cyclopentadienyliron dicarbonyl complex **19** for the olefin C—H functionalization with electrophiles.[25] As a part of reported major work, Fe-complex **19** in combination with $BF_3{*}Et_2O$ and 2,2,6,6-tetramethylpiperidine (TMPH) in toluene was found to be the catalytic system of choice for the diastereoselective higher olefin **18** functionalization with aldehydes **17**, yielding phenylmethanols **20** with medium to good diastereomeric ratios (up to 4.8:1) (Scheme 7). The developed reaction conditions tolerated sensitive functionalities on the alkene moiety, such as a halogen



Scheme 6 Iron-catalyzed azide **14** cyclization.



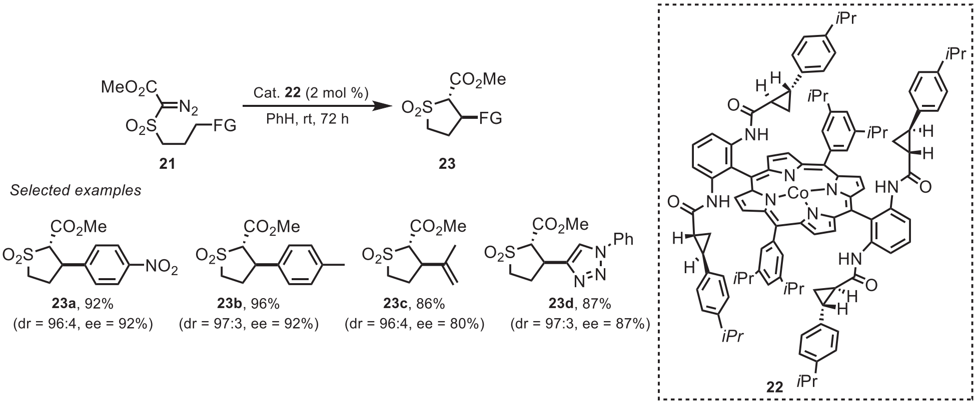
Scheme 7 Iron-catalyzed olefin **18** C—H functionalization with aldehydes.

atom and an amino group, as well as thiophene and boronic acid pinacol ester functionality, allowing to obtain secondary alcohols **20** in good to excellent yields.

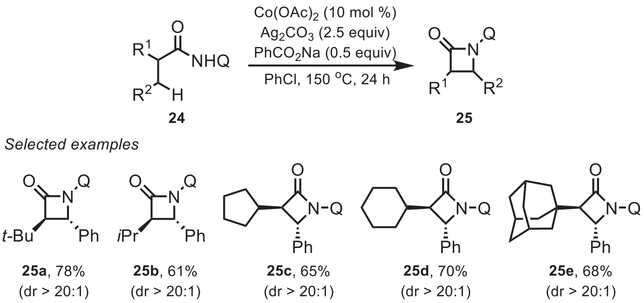
Cobalt

Among other first-row transition metal catalysis, cobalt-catalyzed C—H bond functionalization reactions have experienced enormous interest during past two decades. Despite the fact that the first example on cobalt-catalyzed C—H bond functionalization was demonstrated by Murahashi in 1955,[26] there was a long, dormant period, after which cobalt-catalyzed C—H functionalization was reborn in 2010. Since then, there has been a rapid progress in the development of novel methodologies using cobalt catalysis. Cobalt was considered to be one of the most promising 3d metals for C—H functionalization.[27–33] In this section, we demonstrate the most recent advances for diastereoselective C—H functionalization methodology under cobalt catalysis.

In 2015, Zhang and coworkers reported a stereoselective intramolecular C—H alkylation of diazosulfones **21** *via* Co(II) metalloradical catalysis (Scheme 8).[34] Initially, a variety of cobalt complexes of D_2-symmetric chiral amidoporphyrins were tested, which led to discovery of Co(II) catalyst **22** as the catalyst of choice for the efficient intramolecular C—H alkylation of **21**. The reaction proceeded at the room temperature and tolerated a wide range of electronically different functionalities in substrate **21**, including challenging electron deficient substituents, providing *trans*-sulfolanes **23** in great yields, and with high diastereo- and enantioselectivity (up to 97:3 *dr*, up to 94% *ee*). Additionally, authors demonstrated the applicability of sulfolane derivatives **23** for the construction of quaternary carbon center at α-position to ester functionality using several electrophiles, such as NCS, MeI and others.



Scheme 8 Cobalt-catalyzed cyclization of diazosulfones **21**.



Scheme 9 Cobalt-catalyzed intramolecular amination of amides **24**.

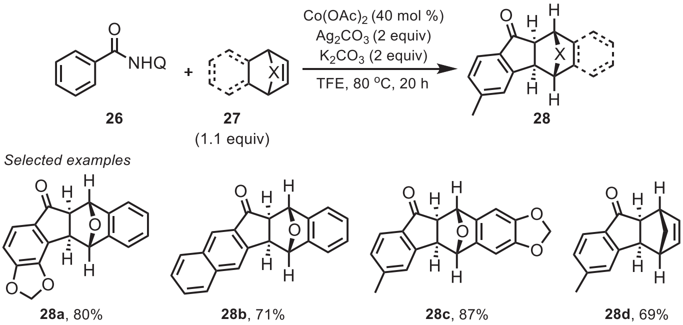
In the same year, Ge and coworkers depicted an elegant methodology for cobalt-catalyzed site-selective dehydrogenative amination of amides 24 (Scheme 9).[35] In their report, authors used $Co(OAc)_2$ catalyst, Ag_2CO_3 oxidant and $PhCO_2Na$ additive in combination with 8-aminoquinoline directing group in PhCl to obtain β-lactams **25** with generally good yields. Interestingly, when α,β-substituted substrates were used, excellent diastereoselectivity of the corresponding products **25** was observed. Moreover, even bulkier substituents like *t*-Bu or adamantane were well-tolerated under optimized reaction conditions and provided β-lactams **25** in high yields and excellent diastereoselectivities.

The diastereoselective [3+2] annulation of benzamides **26** with bicyclic alkenes **27** was demonstrated in 2016 by Cheng and coworkers (Scheme 10).[36] A variety of benzamides **26** with diverse substitution patterns, and different bicyclic alkene coupling partners gave the desired ketones **28** with medium to great yields as single diastereomers. Noteworthy, the insertion of 7-oxabenzonorbornadienes **27** into the C—H activated Co-benzamide complexes occurred only at the *exo* face of alkene, which explains the diastereoselectivity of the developed transformation.

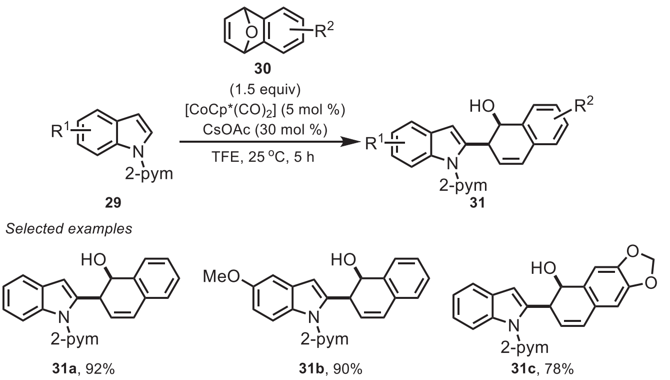
As a continuation to their previous work, Cheng and coworkers in the same year developed a mild approach for a Cp*Co(III)-catalyzed C—H naphthylation of *N*-substituted indoles **29** with 7-oxabicyclic alkenes **30** to yield arylindole derivatives **31** (Scheme 11).[37] Interestingly, in the absence of $AgSbF_6$ additive, at room temperature, authors observed the formation of **31**, however at elevated temperature under acidic conditions the dehydration products were observed. In the reported protocol, formation of the ring-opening products **31** was represented only by five examples, and in every given example product was obtained as a single diastereomer in very high yield.

An interesting approach for cobalt-catalyzed C—H bond annulation of salicylaldehydes **32** with alkynes was demonstrated in 2016 by Yoshikai and Yang (Scheme 12).[38] Under reductive conditions, employing $CoBr_2$ as a catalyst and dcype ligand in combination with Na_2CO_3 and Zn as a reducing agent, four different chroman-4-ones could be obtained with yields up to 81% and medium to good *trans*/*cis* selectivity. Besides, authors note, that in the absence of superstoichiometric amount of zinc the corresponding products could also be obtained, although with significantly diminished yields.

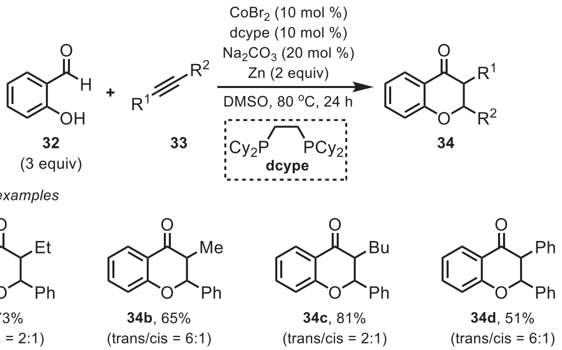
In the same year, Ellman and coworkers demonstrated a highly stereoselective three-component coupling of aromatic C(sp^2)-H bonds of pyrazoles **35**, enones **36** and aldehydes **37** (Scheme 13).[39] Different substitution patterns on the benzene ring moiety were well tolerated. In addition, along with aryl and heteroaryl aldehydes, reactions with more challenging aliphatic and α,β-unsaturated aldehydes also proceeded smoothly. Despite that generally yields of the desired alcohols **38** were moderate to good (51—89% yields), the product's diastereomeric ratio was up to 98:2 *dr*.



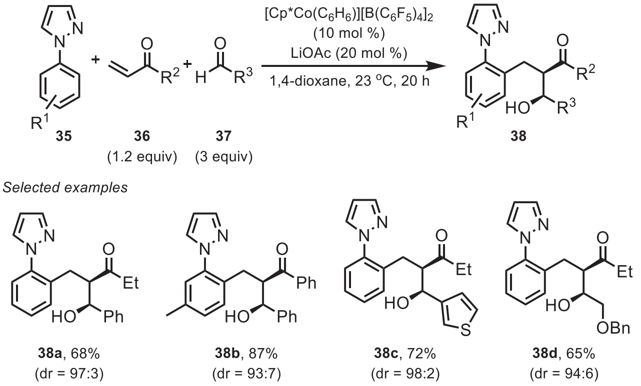
Scheme 10 Cobalt-catalyzed [3+2] annulation of amides **26** with bicyclic alkenes **27**.



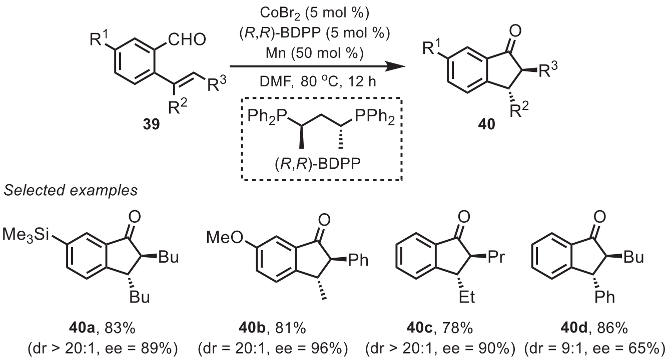
Scheme 11 Cobalt-catalyzed synthesis of arylindoles **31**.



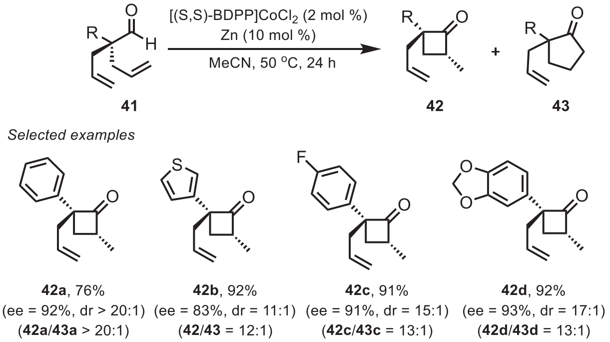
Scheme 12 Cobalt-catalyzed annulation of salicylaldehydes **32** and alkynes **33**.



Scheme 13 Diastereoselective synthesis of alcohols **38**.



Scheme 14 Cobalt-catalyzed intramolecular cyclization of 2-alkenylbenzaldehydes **39**.



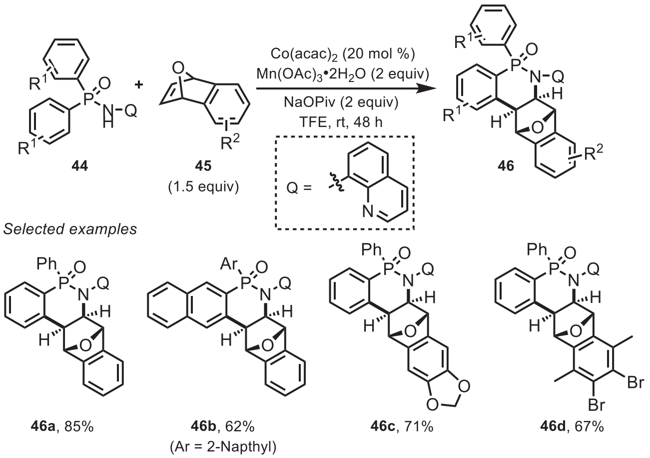
Scheme 15 Cobalt-catalyzed synthesis of cyclobutanes **42**.

In 2017, Yoshikai and coworkers reported an intramolecular diastereo- and enantioselective hydroacylation of 2-alkenylbenzaldehydes **39**, promoted by a chiral phosphine/cobalt catalyst (Scheme 14).[40] According to the mechanism studies, in the proposed catalytic cycle epimerization takes place in intermediates formed from *Z*-alkenes which leads to *trans*-configuration in the product and high diastereoselectivity. Moreover, good to high diastereoselectivity and enantioselectivity was achieved regardless of the *E*/*Z* ratio of the alkenyl group as well as a variety of functional groups in the benzene ring were compatible with the optimized reaction conditions.

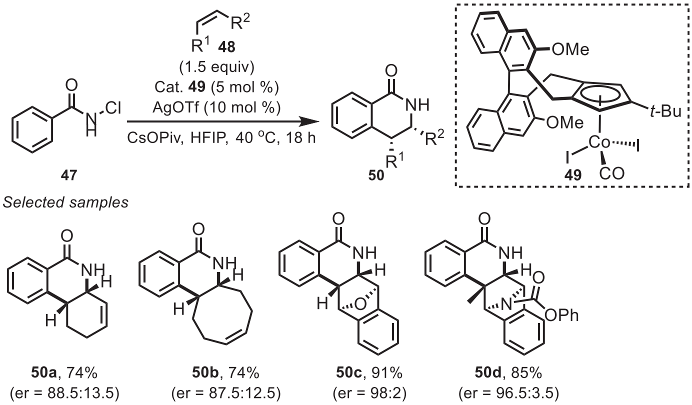
Cyclobutanones bearing α-quaternary carbons are quite challenging to access. In this context, later that year Dong and coworkers demonstrated a similar catalytic system to Yoshikai's method that enabled ring closing thus generating the four-membered ring *via* enantioselective hydroacylation under reductive cobalt catalysis conditions (Scheme 15).[41] While dienyl aldehydes **41** bearing electron-rich α-aromatic groups resulted in high yields and selectivity, substrates with electron-poor α-aromatic groups resulted in somewhat lower enantio- and diastereo-selectivity. Additionally, this synthetic approach may be scaled up with no significant loss both of the product yield and diastereoselectivity.

In 2018, Volla and coworkers depicted their studies on the diastereoselective [4+2] annulation of aryl phosphinamides **44** with heterobicyclic alkenes **45** through cobalt-catalyzed C—H bond activation (Scheme 16).[42] The reaction proceeded in the presence of $Co(acac)_2$ catalyst, $Mn(OAc)_3 \cdot 2H_2O$ oxidant, and sodium pivalate base. Regardless of the electronic effects and steric factors in reaction with a variety of heterobicyclic alkenes **45**, different diarylphosphinamides **44** afforded cyclic products **46** in good to excellent yields as single diastereomers. In addition, authors were able to determine the structure of few products using a single crystal X-ray diffraction analysis, which clearly indicated thermodynamically more favorable *exo* isomer of the products.

In 2019, Cramer and coworkers reported an excellent example on asymmetric C—H bond functionalization of *N*-chlorobenzamides **47** with alkenes **48** providing an efficient access to a broad range of dihydroisoquinolones **50** (Scheme 17).[43] The optimization of the reaction conditions revealed that the developed and synthesized chiral trisubstituted cyclopentadienyl cobalt(III)



Scheme 16 Cobalt-catalyzed [4+2] annulation of phosphinamides **44** with alkenes **45**.

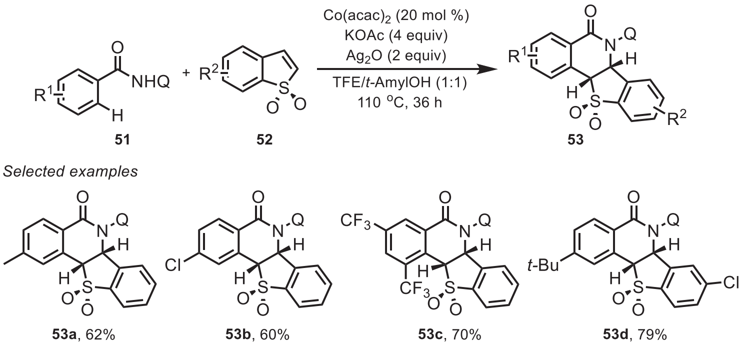


Scheme 17 Cobalt-catalyzed synthesis of dihydroisoquinolones **50**.

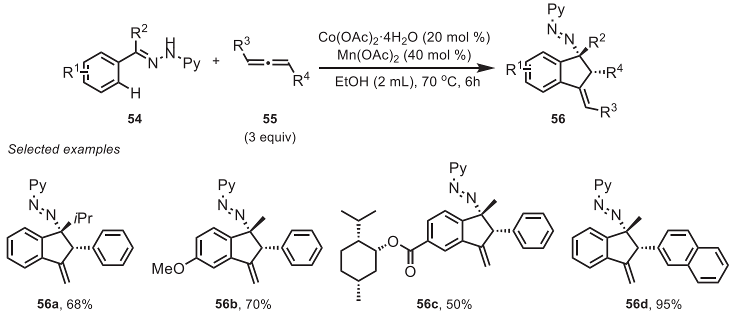
complex **49** in combination with AgOTf and CsOPiv in HFIP could deliver the desired products **50** in good yields and with high enantiomeric ratios. Noteworthy, it was observed, that silver triflate was not mandatory for the reaction, although the absence of additive slightly reduced the yield. While diastereoselective reactions were performed with only 4 disubstituted alkenes, authors showed a large quantity of examples for the synthesis of monosubstituted isoquinolones **50** with yields up to 91%, and enantiomeric ratios of products up to 99.5:0.5.

In the same year, Kathiravan, Nicholls and coworkers reported the synthesis of annulated benzothiophenedioxides **53** through a diastereoselective C—H bond functionalization catalyzed by Co(acac)$_2$ (Scheme 18).[44] Both electron-rich and electron-deficient amides **51** were able to provide corresponding annulation reaction products **53** in good yields as single diastereomers, whereas heterocyclic and alkenyl amides did not participate in this reaction. Importantly, 8-aminoquinoline directing group was crucial for the developed transformation, as other frequently used directing groups such as pyridine *N*-oxide or phenyl oxazoline proved to be ineffective.

Two years later, a cobalt-catalyzed C—H activation and [3+2] annulation of hydrazones **54** with allenes **55** was demonstrated by Volla and Dey, allowing to obtain indane **56** derivatives in a diastereoselective fashion (Scheme 19).[45] It is worth mentioning, that in their study the active cobalt catalyst was regenerated using air as a green oxidant, while Mn(OAc)$_2$ was the co-oxidant. Both electron-withdrawing and electron-donating substituents on the benzene ring moiety were compatible under carefully optimized reaction conditions, delivering a diverse range of indanes **56** in moderate to very good yields (up to 95%) as single diastereomers.



Scheme 18 Cobalt-catalyzed benzamide **51** annulation with benzothiophene dioxide **52**.



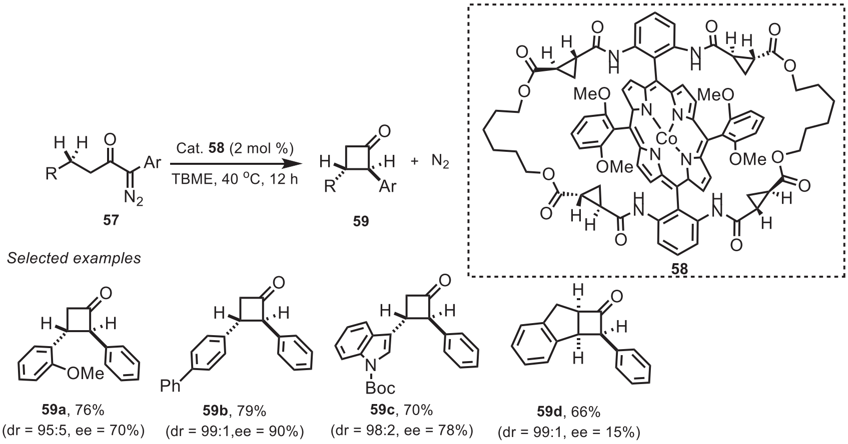
Scheme 19 Cobalt-catalyzed hydrazone **54** annulation with allenes **55**.

Additionally, a few bioactive molecules, for example L-menthol-substituted hydrazone, also underwent the annulation to afford the corresponding product **56c** in moderate yield. Moreover, authors were able to selectively reduce the internal double bond, delivering another stereocenter.

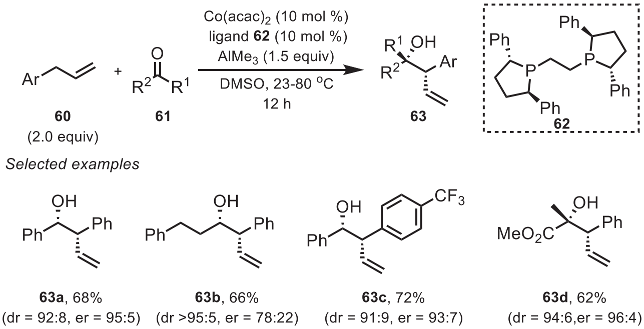
In 2021 Zhang and his research group reported their work on the cobalt-catalyzed asymmetric 1,4-C-H alkylation of α-diazoketones **57** to construct chiral cyclobutanones **59** (Scheme 20).[46] The key step of the reaction is hydrogen atom abstraction by free radicals, which is considered as one of the most general pathways for C—H activation step. Using a new-generation D_2-symmetric chiral amidoporphyrin cobalt(II) complex **58**, the substrate scope was evaluated with 1,4-diaryl-α-diazoketones **57** containing 4-aryl substituents with various steric and electronic properties. As a result, a broad variety (21 examples) of cyclobutanones **59** was obtained in good to excellent yields (up to 93%) and with remarkable diastereo- and enantioselectivity (up to 99:1 *dr*, up to 96% *ee*). Moreover, authors conducted a series of mechanistic experiments, both experimental and computational, to study the reaction mechanism in details, and additionally, synthetic transformations of the obtained products **59** were demonstrated in order to access a wide variety of synthetically useful compounds.

A novel methodology for the cobalt-catalyzed diastereo- and enantioselective allyl addition to aldehydes and ketoesters was published by Meng and coworkers in 2021 (Scheme 21).[47] According to proposed hypothesis, initially nucleophilic allyl-Co species are generated followed by diastereo- and enantioselective addition to aldehydes or ketoesters **61** thus furnishing a variety of homoallylic alcohols **63**. Optimization of the reaction conditions was conducted, indicating that ligand **62** was the most suitable for developed transformation, improving diastereo- and enantioselectivity without significant loss of product yield. Various substituents containing aldehydes and ketoesters **61** were investigated in allylic C—H functionalization reaction, delivering the desired products **63** in generally medium yields, although with high enantiomeric and diastereomeric ratios. Interestingly, reactions with allylbenzenes **60** containing electron-withdrawing groups proceeded even at room temperature while retaining efficiency and selectivity.

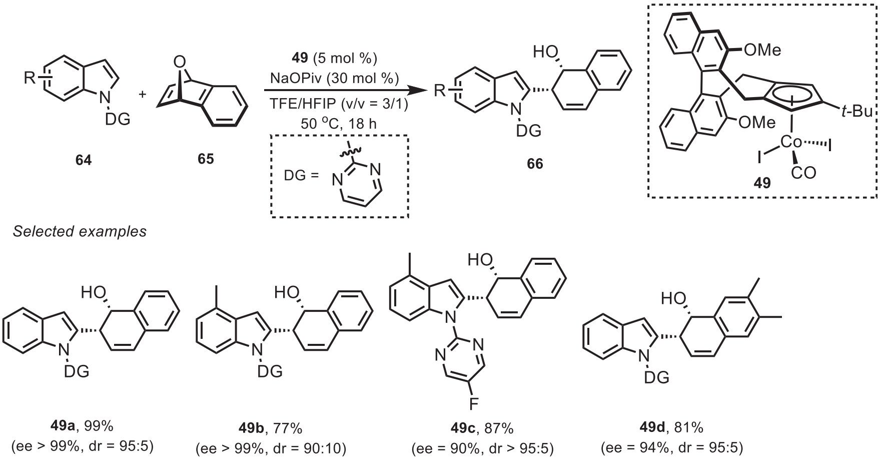
Asymmetric ring opening of 7-oxabenzonorborandienes **65** *via* indole **64** C—H activation was demonstrated by You and coworkers in 2022 (Scheme 22).[48] Interestingly, during optimization of reaction conditions TFE as a solvent showed great potential yielding product **66** with high diastereo- and enantioselectivity, although the reaction yield was moderate. On the other hand, HFIP as a solvent improved the reaction yield, but a slight decrease in products' **66** diastereomeric ratios and enantioselectivity was



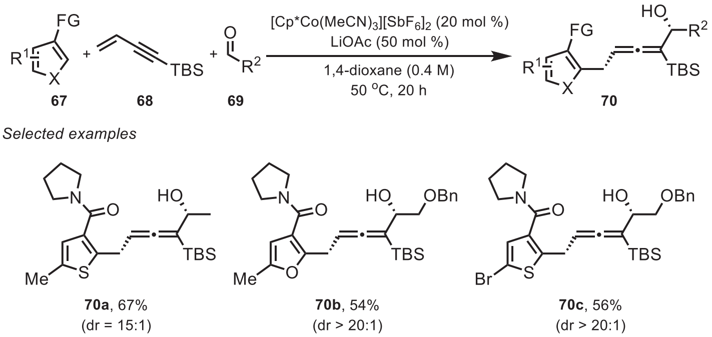
Scheme 20 Cobalt-catalyzed synthesis of cyclobutanones **59**.



Scheme 21 Cobalt-catalyzed allyl addition to carbonyl compounds **61**.



Scheme 22 Cobalt-catalyzed asymmetric ring-opening of 7-oxabenzonorbornadienes **65** via indole C—H functionalization.



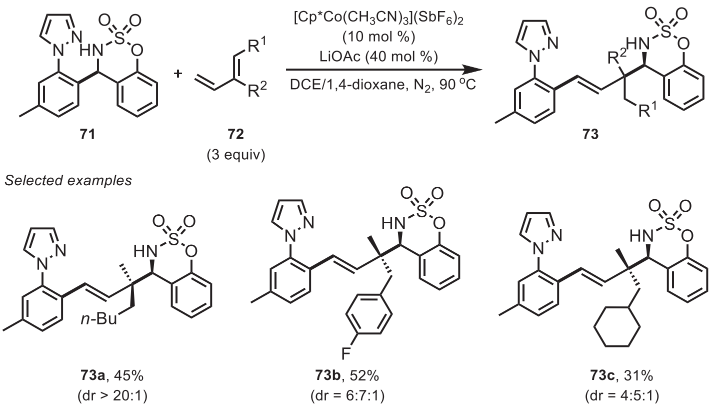
Scheme 23 Cobalt-catalyzed synthesis of allenyl alcohols **70**.

observed, which explains the use of combination of both solvents in optimized conditions. Authors were able to provide significant substrate scope with a diverse variety of functional groups in both indoles **64** and 7-oxabenzonorbornadienes **65**, delivering indole derivatives **66** in poor to excellent yields (25—99%) with generally great enantio- and diastereo-purity.

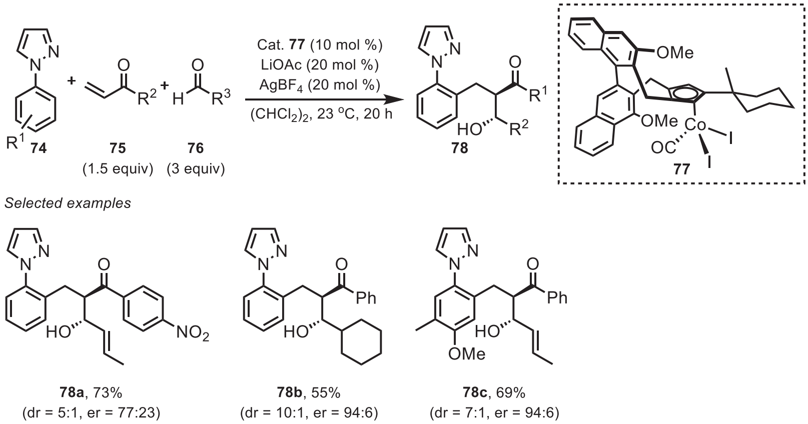
In the same year, Ellman and coworkers reported highly stereoselective synthesis of synthetically useful allenyl alcohols **70** under Cp*Co catalysis (Scheme 23).[49] In reported methodology a broad scope of substrates **67**, 1,3-enynes **68** and aldehydes **69** was investigated for the three-component coupling reaction, yielding corresponding alcohols **70** in medium to great yields and in a highly diastereoselective fashion. It was proposed that due to the large size of Cp* ligand, alkyne and aldehyde substituents point away from cobalt in the transition state resulting in diastereoselective propargyl addition.

In 2022, Xu and Shi developed a Co(III)-catalyzed divergent functionalization of *N*-sulfonylamines **71** *via* β-carbon elimination (Scheme 24).[50] The proposed reaction mechanism of this spectacular transformation suggests that after initial ligation with cobalt catalyst, *N*-sulfonyl imine is separated due to β-carbon elimination. Subsequent migratory insertion of diene **72** leads to the double-bond migration, which results in an intermediate that can trap the imine fragment and generate the insertion-type product **73**. In this context, a variety of 1,2-disubstituted dienes **72** and different sulfonylamines **71** proved to be suitable components for the developed transformation, delivering the corresponding products **73** in good to great yields. Despite that, the diastereoselective version of this methodology was demonstrated only by five examples with generally good diastereoselectivity.

In 2023, Cramer and coworker described a highly enantio- and diastereoselective three-component coupling for the generation of β-hydroxyketones **78** through cobalt catalysis (Scheme 25).[51] Both electron-withdrawing and electron-donating groups in reaction components were well-tolerated and had no or little influence on the reaction, liberating the formation of **78** in generally good yields (43—77%) with great enantiopurity and diastereomeric excess. Noteworthy, the installation of a bulky methylcyclohexane substituent on the Cp* ligand of the Co(III) catalyst **77** was the key element for successful reaction and high level of selectivity.



Scheme 24 Cobalt-catalyzed diastereoselective functionalization of *N*-sulfonylamines **71**.



Scheme 25 Cobalt-catalyzed three-component coupling for the synthesis of β-hydroxyketones **78**.

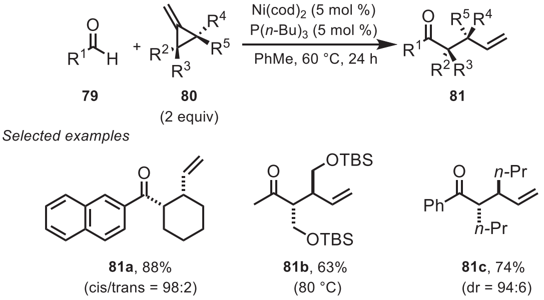
Nickel

Twice as abundant as copper, nickel constitutes about 0.007% of Earth's crust being found in both terrestrial as well as meteoric deposits. Since its isolation and classification in 18th century, nickel has been used in coinage, alloy materials, batteries and of course transition metal catalysis. With fine tuning of ligands, nickel catalysts have demonstrated outstanding ability to activate and coordinate unsaturated organic molecules, mediating transformations of π-electronic systems, with notable achievements in cyclizations, cycloaddition reactions and multi-component couplings.[52−55] Herein, a few examples on diastereoselective nickel-catalyzed C−H bond functionalization will be disclosed.

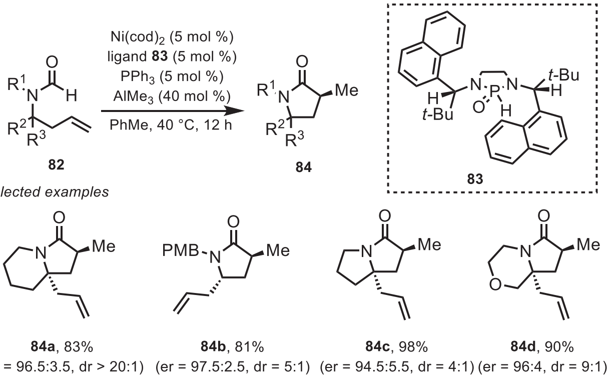
In 2009, Ohmura, Suginome and coworker depicted novel nickel-catalyzed intermolecular hydroacylation of methylenecyclopropanes **80** (Scheme 26).[56] Authors found that using Ni(cod)$_2$ catalyst and achiral phosphine ligand, the reaction proceeded *via* a stereospecific opening of the cyclopropane **80** ring to give γ,δ-unsaturated ketones **81** in overall good yields. Various methylenecyclopropanes **80** reacted with corresponding aldehydes **79** in a highly stereospecific manner, giving corresponding ketones **81** with high *trans*/*cis* selectivity depending on substitution pattern in cyclopropanes **80**, and with high diastereomeric purity (up to *dr* 94:6).

A few years later, in 2013, Cramer and coworker reported an asymmetric hydrocarbamoylation of homoallylic formamides **82** *via* nickel catalysis, employing a novel class of chiral diaminophosphineoxide ligands (Scheme 27).[57] Different functionalities on the formamide **82** and at α-position to amide were successfully tolerated under the reported conditions and gave the desired pyrrolidines **84** in very good yields (up to 98%) with high enantiopurity. The observed diastereoselectivity for the transformation ranged from 4:1 to >20:1.

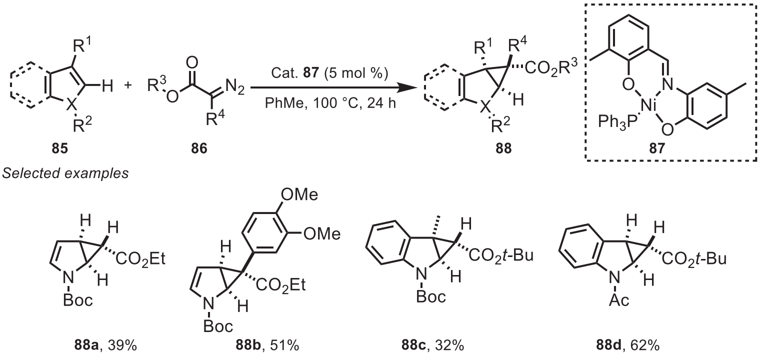
In 2020, Mondal, Roy and coworkers reported a Schiff base-Ni(II)-phosphine-catalyzed chemodivergent C−H functionalization and cyclopropanation of aromatic heterocycles (Scheme 28).[58] Interestingly, the introduction of a suitable electron-withdrawing group such as Boc or acetyl group with the aim to reduce overall electron density over the C2 = C3 double bond of a heterocycle **85** changed the reaction course from C2 or C3 functionalization to C2/C3 cyclopropanation. The cyclopropanation products **88**



Scheme 26 Nickel-catalyzed ring-opening hydroacylation of methylenecyclopropanes **80**.



Scheme 27 Nickel-catalyzed intramolecular cyclization of alkenes **82**.



Scheme 28 Nickel-catalyzed C—H functionalization and cyclopropanation of heterocycles **85**.

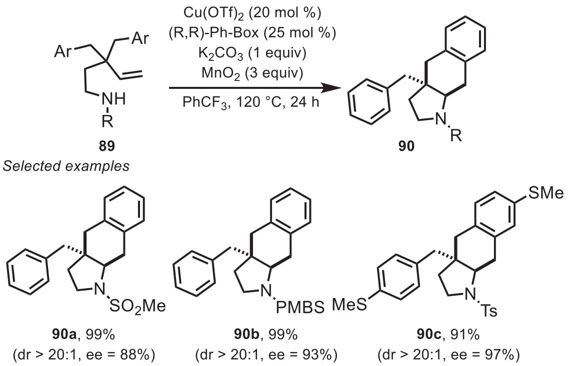
were obtained with excellent *exo*-diastereoselectivity, although in mediocre yields (25—65%). In case of *t*-Bu diazoacetate, the *exo*-cyclopropanated products formed exclusively because of the increased steric bulkiness offered by the *t*-Bu group.

Copper

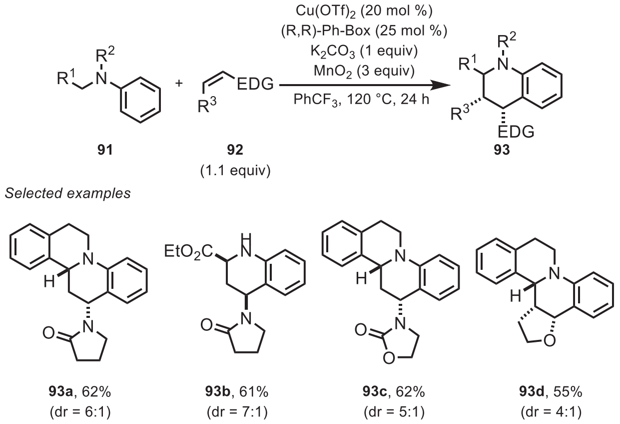
Copper is the fourth most earth-abundant transition metal that occurs in nature in the form of ores and in a directly useable metallic form. The diversity of copper chemistry is due to its variable and interchangeable oxidation state, capacity to coordinate with heteroatoms, and the ability to activate terminal alkynes with several other bonding modes such as C—O, C—S, etc. also being explored. Nowadays, numerous copper-catalyzed reactions such as amination and ether formation from aryl halides and related compounds, aziridination of olefins, "click-chemistry," hydrosilylation reactions, additions to carbonyl and α,β-unsaturated carbonyl compounds, etc. have become useful tools for organic synthesis. Copper can be exploited as a cross coupling metal catalyst and a good alternative to palladium due to its strikingly similar reactivity and chemoselectivity.[59—63]

A new method for the enantioselective synthesis of hexahydro-1*H*-benz[*f*]indoles **90** was described by Chemler and coworkers in 2010 (Scheme 29).[64] The copper-catalyzed intramolecular alkene **89** carboamination process proved to be effective for installation of vicinal tertiary and quaternary carbon stereocenters with high levels of diastereo- and enantioselecitivity. Various aryl-substituted as well as *N*-arylsulfonyl- substituted substrates **89** provided corresponding hexahydro-1*H*-benz[*f*]indole adducts **90** in excellent yields and with high selectivity. Interestingly, authors observed that substrates **89** bearing an *o*-aryl substituent as a reaction product gave two regioisomers from which one was the result of *ipso*-addition followed by 1,2-alkyl shift.

In 2014 Seidel and coworkers found that iminium ions generated in situ *via* copper catalyzed oxidation of *N*-aryl amines **91** readily undergo [4+2] cycloadditions with a range of dienophiles **92** (Scheme 30).[65] The method involves functionalization of both C(sp^3)-H and C(sp^2)-H bonds resulting in polycyclic amines **93** under relatively mild conditions. The scope of the oxidative Povarov reaction was evaluated with a range of acyclic and cyclic enol ethers and enamide dienophiles. Corresponding substituted tetrahydroisoquinolines **93** were obtained in moderate to good yields with generally medium diastereoselectivity.



Scheme 29 Copper-catalyzed intramolecular alkene **89** carboamination.

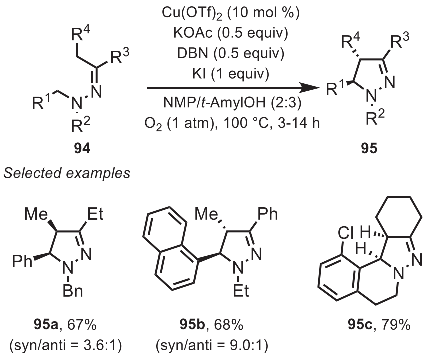


Scheme 30 Copper-catalyzed synthesis of polycyclic amines **93**.

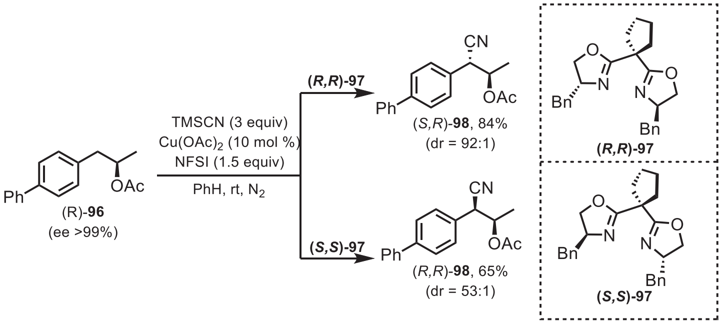
A highly diastereoselective aerobic copper-catalyzed intramolecular dehydrogenative cyclization of *N*,*N*-disubstituted hydrazones **94** was developed by Ge and coworkers in 2015 (Scheme 31).[66] Aromatic, acyclic and cyclic aliphatic hydrazones **94** were compatible under the oxidative reaction conditions and yielded *syn*-isomers as the major reaction products in moderate to high yields. In substrates where *N*-benzyl group (R^2) was replaced with an alkyl group, aromatic hydrazones **94** favored the formation of *anti*-isomers of **95**, while aliphatic substrates favored the *syn*-isomers of **95**, providing an important and tunable strategy to selectively access either *anti* or *syn* pyrazolines **95**. The observed diastereoselectivity was rationalized by a 5-center/6-electron disrotatory cyclization mechanism which was supported by performed computational studies.

One year later, Stahl, Liu and coworkers reported novel methodology on enantioselective cyanation of benzylic C—H bonds *via* copper-catalyzed radical relay. In their report on enantioselective cyanation of C(sp^3)-H bonds, reaction selectivity studies were done using enantiomerically pure homobenzylic acetate (R)-**96** (Scheme 32).[67] Copper catalyst was tested with each of the ligand **97** enantiomers and in both cases products were obtained in good yields with excellent diastereoselectivity, reflecting high levels of catalyst-rather than substrate-controlled stereoselectivity. Additionally, authors attributed the minor difference on product yields and diastereomeric ratios to a matched-mismatched effect between the substrate chirality and the ligand.

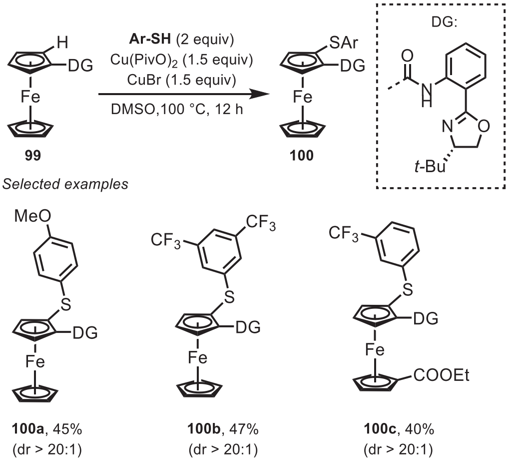
The first copper-mediated diastereoselective C—H thiolation of ferrocenes **99** was developed by Dai, Yu and coworkers in 2018 (Scheme 33).[68] Oxazoline directing group bearing a *t*-Bu substituent was essential to achieve the resulting diastereoselectivity of the product **100**. The high diastereoselectivity and mono-vs dithiolated product ratio was rationalized through the conformational analysis by comparing *t*-Bu/methyl/*i*Pr and phenyl substituted oxazolines as the directing groups. It was concluded, that bulkier *t*-Bu group positions above the tethered ferrocene plane with high conformational ratio thus rendering its excellent diastereoselectivity. Moreover, authors note, that due to the steric repulsion after monothiolation, the formation of dithiolated product is



Scheme 31 Copper-catalyzed cyclization of hydrazones **94**.



Scheme 32 Catalyst-controlled stereoselective homobenzylic acetate (R)-**96** cyanation reaction.



Scheme 33 Copper-catalyzed thiolation of ferrocenes **99**.

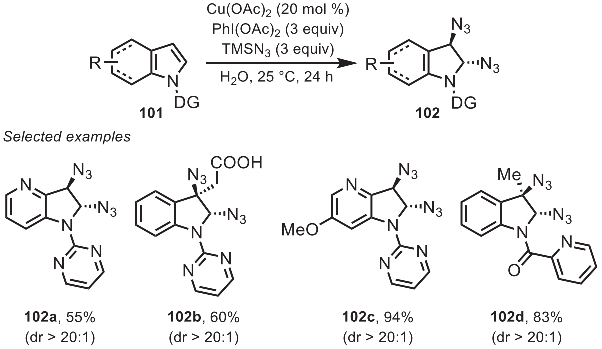
suppressed. A series of arylthiols were competent reaction partners and gave corresponding ferrocenes **100** with moderate yields (36—55%) in a highly diastereoselective manner (*dr* > 20:1).

In 2019 Zhu and coworkers developed a copper-catalyzed directed dearomatization of indoles **101** (Scheme 34).[69] With assistance of directing group, copper-catalyzed reaction between trimethylsilyl azide and indoles **101** provided 2,3-diazido indolines **102** in good yields and excellent diastereoselectivity (*dr* > 20:1). A range of substituted indoles **101** containing 2-pyrimidyl directing group were investigated and products **102** were obtained in moderate to excellent yields (44—90%). Additionally, 2-picolinamide directing group was studied, which most likely coordinates with $Cu(OAc)_2$ and forms a six-membered ring structure leading to product formation.

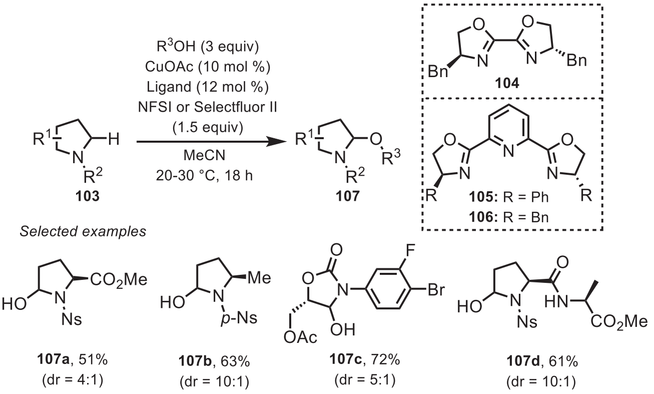
In 2021, Wang, Zhao and coworkers reported a Cu(I)-catalyzed late-stage C(sp^3)-H α-functionalization of *N*-heterocycles **103** (Scheme 35).[70] The developed protocol was successfully applied to a broad substrate scope yielding 34 compounds, including eight different types of *N*-heterocycles which are usually found as skeletons in pharmaceuticals and natural products. Modification of the reaction conditions by changing the reaction ligand and *N*—F reagent allowed to find appropriate conditions for all the *N*-heterocycles investigated, yielding the desired products **107** in moderate to excellent yields (41—97%). However, only six examples for diastereoselective transformation were demonstrated, delivering the desired products in poor to medium diastereoselectivities (1:1 to 10:1 *dr*). Additionally, authors demonstrated, that the obtained products **107** could be successfully further used for late-stage alkylation reaction.

Second Row Transition Metals

The most common catalysts for C—H bond functionalization reactions are second-row transition metals. Precisely due to the stability of second-row transition metal intermediates, C—H functionalization mechanisms have been investigated and proposed. Despite the nowadays efforts to develop methodology using abundant first-row transition metals, second-row transition metals are



Scheme 34 Copper-catalyzed dearomatization of indoles **101**.



Scheme 35 Copper-catalyzed α-functionalization of *N*-heterocycles **103**.

still required for efficient C(sp^3)—H bond functionalization, meta-selective C(sp^2)-H functionalization and late stage transformations.[1–7]

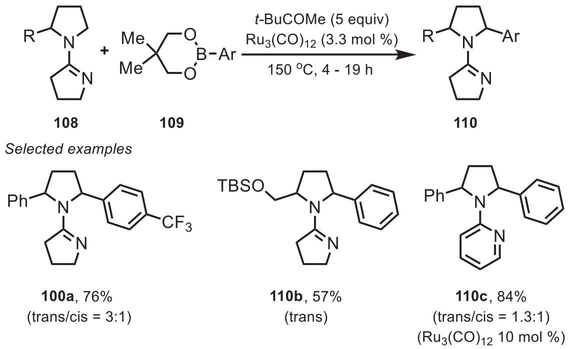
Ruthenium

Ruthenium exists in various stable oxidation states (II, III, IV and VII), that can be linked with auxiliary ligands of various geometries to form Ru complexes with diverse electronic and steric properties. Various ruthenium compounds have promising applications in catalysis and their low toxicity tends to make them an ideal option for catalytic drug synthesis. These characteristics, together with the fact that ruthenium compounds are less expensive than other noble metal compounds (Pd, Pt, Rh, and Ir), have made them as catalysts of choice for many catalytic reactions, including C—H bond activation and functionalization.[71–75]

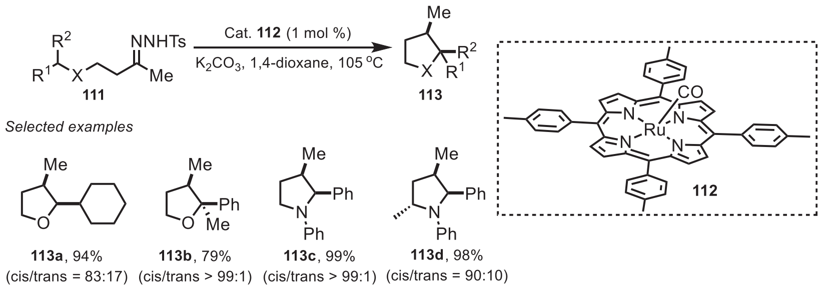
Sames and coworkers in 2006 proposed a methodology for ruthenium-catalyzed arylation reaction of pyrrolydine **108** with arylboronate esters **109** (Scheme 36).[76] Successful reaction required dihydropyrrole as a directing group and $Ru_3(CO)_{12}$ as catalyst. As a result, substrates **108** containing both electron-donating and electron-withdrawing substituents as well as TBS-protected prolinol underwent successful arylation under the developed catalytic conditions. Noteworthy, relatively poor *trans*/*cis* stereoselectivity in some arylation examples was explained by the isomerization of product **110** under the reaction conditions (subjection of each product **110** stereoisomer to the reaction conditions resulted in isomerization, which was more rapid than the arylation reaction). Nevertheless, the methodology reported is operationally simple and the isomers are readily separable by column chromatography.

Almost 10 years later, Che and coworkers reported that by employing ruthenium-porphyrin catalyst **112**, alkyl diazomethanes generated in situ from *N*-tosylhydrazones **111** led to a Ru carbene intermediate that underwent intramolecular C(sp^3)-H insertion to give substituted tetrahydrofurans and pyrrolidines **113** (Scheme 37).[77] Various *N*-tosylhydrazones **111** derived from β-alkoxy ketones and aldehydes underwent cyclization reaction to give the corresponding cyclic products **113** in moderate to good yields (up to 99%) with great diastereoselectivity (up to >99:1 *cis*/*trans*). Interestingly, product **113b** containing quaternary carbon center was obtained with complete retention of configuration from its optically active *N*-tosylhydrazone substrate **111b**.

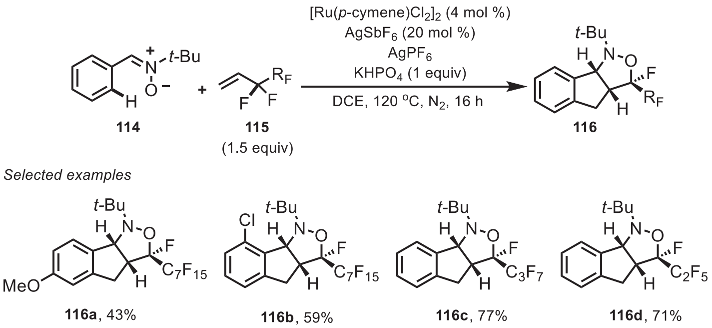
In 2018, Li and coworkers investigated the ruthenium-catalyzed coupling of aryl nitrones **114** and perfluoroalkyl substituted alkenes **115** toward the synthesis of fluorinated isoxazolidines **116** (Scheme 38).[78] During initial optimization of reaction conditions, they found that Ru catalyst showed superior reactivity and selectivity compared to Rh, Co, and Mn catalysts. Moreover, the use



Scheme 36 Pyrrolydine **108** arylation with arylboronate esters **109** using $Ru_3(CO)_{12}$.



Scheme 37 Ruthenium-catalyzed cyclization of *N*-tosylhydrazones **111**.

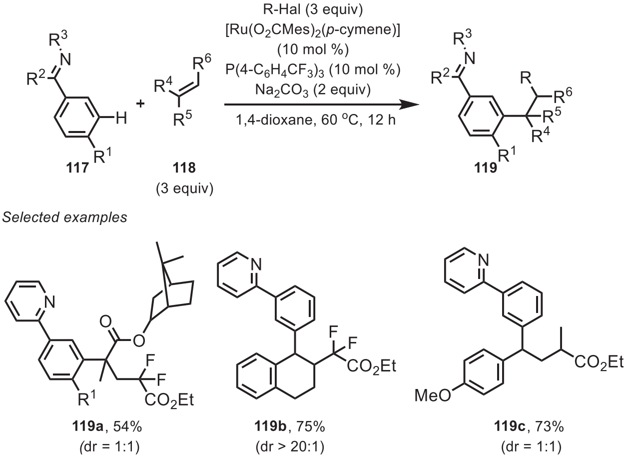


Scheme 38 Ruthenium-catalyzed aryl nitrone **114** and perfluoroalkyl-substituted olefin **115** coupling reaction.

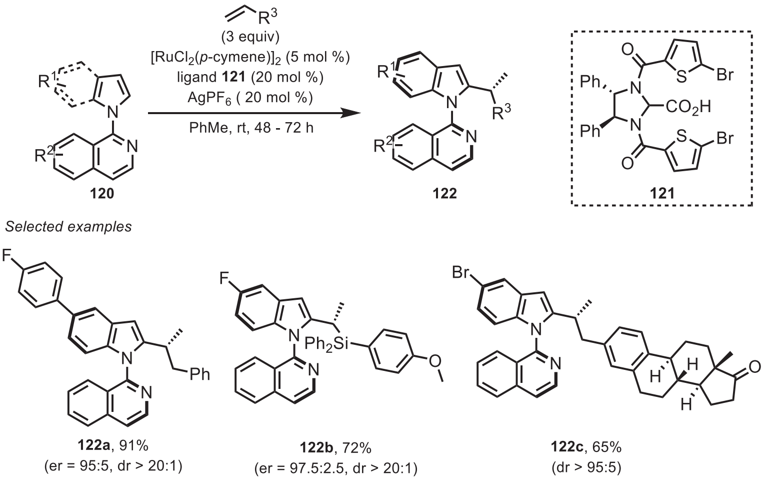
of AgSbF$_6$ and K$_2$HPO$_4$ as additives had a significant impact on the reaction regioselectivity and product yield. The authors explored the scope and generality of this coupling system and found that diverse substitution pattern containing nitrones **114** and various perfluoroalkylalkenes **115** underwent smooth coupling with high efficiency, leading to the formation of fused isoxazolidines **116** in excellent regio- and diastereoselectivity.

One year later, in 2019, Liang and coworkers described an efficient and versatile three-component *meta*-selective C—H functionalization of various arenes **117** using substituted alkenes **118** and various halides (Scheme 39).[79] Under optimized reaction conditions, the transformation showed to be effective for a wide range of substrates **117** and produced bioactive 1,1-diarylalkanes and other challenging products in good to excellent yields. The reaction scope was expanded to include different directing groups and aliphatic as well as internal alkenes. Despite that, only few examples represent diastereoselective nature of the reaction. Although in some cases selectivity exceeded 10:1 diastereomeric ratio, majority of products were obtained with poor diastereoselectivity ranging from 1:1 to 6:1 *dr*.

The development of a highly efficient and regio-, diastereo-, and enantioselective ruthenium(II)-catalyzed C—H alkylation system using novel C2-symmetric chiral imidazolidine carboxylic acids as ligands was reported by Ackermann and coworkers in 2022 (Scheme 40).[80] Optimized ligand **121** was used to explore the scope of the catalytic system using diverse substitution pattern bearing indoles **120** and alkenes, which were proven to be competent substrates, providing products **122** with high yields along with impressive enantioselectivity and diastereoselectivity. The method also showed good tolerance to diverse functional groups and offered an attractive strategy for the facile modification of natural products or drug molecules.



Scheme 39 Multicomponent coupling reaction between halides, **117** and **118** employing ruthenium catalysis.



Scheme 40 Ruthenium-catalyzed indole **120** alkylation.

Rhodium

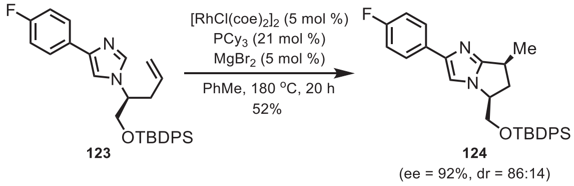
Rhodium is one of the most exploited transition metals in catalysis, since it favors a wide range of chemical transformations that are fundamental for the organic synthesis, both in laboratory reactions and industrial processes. Rhodium has demonstrated not only a unique capability to mediate C—H bond activation and subsequent reactions with various reactive coupling partners such as alkenes, allenes, alkynes and isocyanides, but also a broader functional group tolerance if compared to ruthenium or other transition metals (if nitrogen containing directing groups are used). Besides, rhodium catalysts have been successfully exploited for various asymmetric C—H functionalization processes allowing access to various classes of products in a diastereoselective manner with excellent enantioselectivities.[81–85] This section consists of selected examples for diastereoselective C—H functionalization by some of the key contributors in this field.

In 2007, synthesis of bicyclic bisarylimidazole *N*-terminal kinase 3 inhibitors was achieved using diastereoselective rhodium-catalyzed cyclization by Bergman, Ellman and coworkers (Scheme 41).[86] Treatment of enantiomerically pure alkene starting material **123** with $[RhCl(coe)_2]_2$ catalyst in the presence of PCy_3 ligand and $MgBr_2$ at 180 °C provided the bicyclic arylimidazole **124** with 86:14 diastereomeric ratio and enabled the isolation of the product with enantiomeric access of 92%.

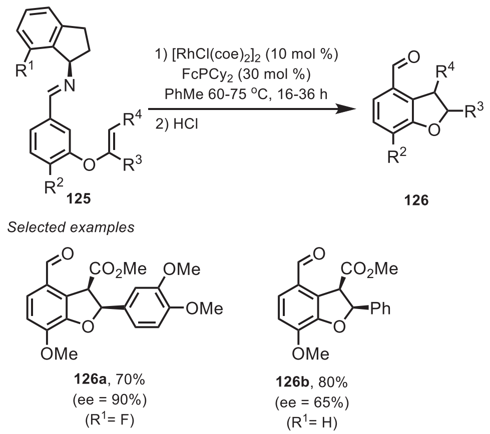
In the same year, Bergman, Ellman and coworkers demonstrated asymmetric intramolecular alkylation of chiral aromatic imines **125** using $[RhCl(coe)_2]_2$ catalyst with ferrocenyl-PCy_2 ligand (Scheme 42).[87] The 7-substituted 2-aminoindanes, which served as the directing groups, were condensed with aldehydes to obtain chiral imines **125** that after rhodium-catalyzed intramolecular alkylation and hydrolysis led to dihydrobenzofurane products **126**. Products **126** were obtained with excellent diastereoselectivity yielding *cis*-product **126** as the only isomer, except for **126a**, where trace amounts of trans-diastereomer were detected. Product enantiopurity for the developed reaction ranged from 55 to 90% ee.

The same rhodium catalyst was used by Bergman, Ellman and Tsai in the total synthesis of (−)-Incarvillateine. Diastereoselective intramolecular alkylation of **127** was used as a key step toward the monoterpene alkaloid, which has potent analgesic properties (Scheme 43).[88] Although many ligands tested for cyclization of **127** gave product **128** in quantitative yield, (DMAPh)-PEt_2 was the most selective ligand and provided diastereomers **128a** and **128b** in a diastereomeric ratio of 83:17.

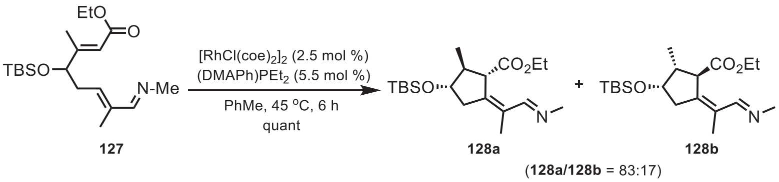
Continuing their work on the strategy for the assembly of pharmaceutically relevant classes of nitrogen heterocycles from simple and readily available precursors, Bergman, Ellman and coworkers reported a versatile reaction cascade leading to highly substituted



Scheme 41 Rhodium-catalyzed synthesis of bicyclic arylimidazole **124**.

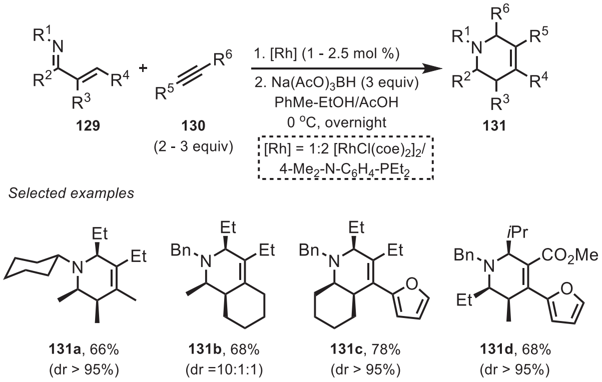


Scheme 42 Rhodium-catalyzed itramolecular cyclyzation of imines **125**.



Scheme 43 Rhodium-catalyzed olefinic C–H bond activation in **127**.

1,2,3,6-tetrahydropyridines **131** (Scheme 44).[89] Rhodium-catalyzed β-C-H bond activation of α,β-unsaturated imines **129** followed by the addition of alkynes **130** gave azatriene intermediates, which underwent electrocyclization in situ to give 1,2-dihidropyridines that were selectively reduced to obtain substituted tetrahydropyridines **131**. In this context, Na(AcO)$_3$BH under acidic conditions was required for clean and highly diastereoselective reduction. A diverse set of imines **129**, including *N*-substituted ones, and alkynes **130** were evaluated. All of the obtained hexasubstituted products **131** showed exclusive diastereoselectivity with only a single diastereomer detectable by ^{1}H and ^{13}C spectroscopy, except for the bicyclic product **131b** for which 10:1:1 ratio of stereoisomers was observed.

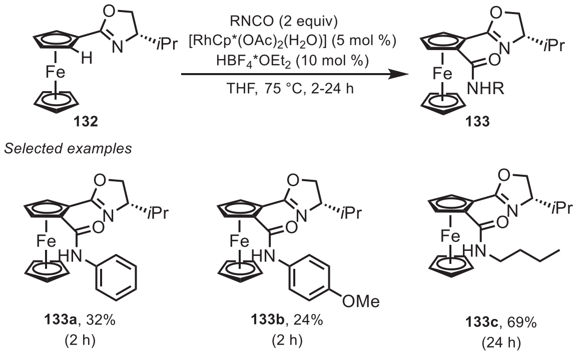


Scheme 44 Rhodium-catalyzed synthesis of tetrahydropyridines **131**.

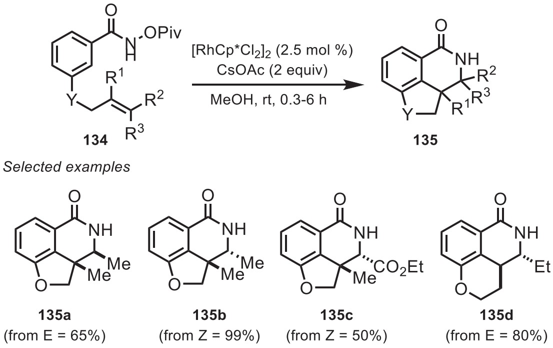
At the same time, using rhodium-catalyzed C—H activation of ferrocene derivatives **132**, Shibata and coworkers were able to produce a variety of 1,2-disubstituted ferrocene derivatives **133** in a highly diastereoselective fashion (Scheme 45).[90] Chiral oxazolyl ferrocene **132**, which is commercially available, was reacted with differently substituted isocyanates under Cp*Rh(III) catalysis conditions and resulted in a variety of planar chiral products **133** as single diastereomers in generally medium yields due to the low reaction conversion.

In 2013, Rovis research group found three distinct Rh(III)-catalyzed reaction pathways for tethered olefin-containing benzamide C—H bond functionalization.[91] Hydroarylation, amidoarylation and dehydrogenative Heck-type products can be accessed depending on the type of benzamide substrate used. Intramolecular amidoarylation along with hydrolysis of the starting material resulted in product **135**. Moreover, olefin geometry was of great importance, since depending on substrate **134** double bond configuration, reaction produced opposite diastereomers, respectively, *E*-alkenes produced *cis*-stereochemistry and *Z*-alkenes produced *trans*-isomers (Scheme 46). A broad substrate **134** scope was demonstrated bearing electron-poor, as well as electron-rich substituents. Interestingly, *E*-1,1-disubstituted alkene **134d** cyclized to solely give the *trans* product **135d** in good yield.

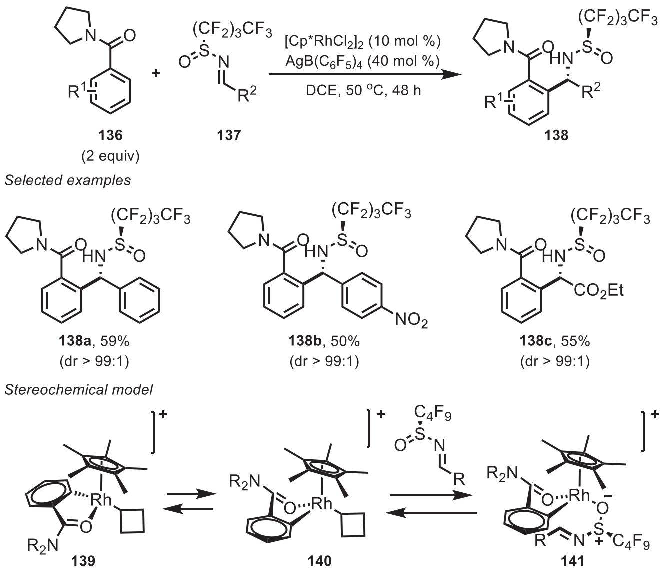
The first asymmetric intermolecular addition of non-acidic C—H bonds to imines was reported by Ellman and coworkers in 2014 (Scheme 47).[92] A cationic Rh(III) catalyst was used for the directed addition of aromatic C—H bonds to *N*-perfluorobutanesulfinyl imines **137**. Authors accented that the imine **137** substituent was essential for achieving sufficient reactivity and high diastereoselectivity for the developed transformation. Reaction was performed with a variety of substituted benzamides **136** and imines **137** yielding products **138** in moderate yields, but exceptional diastereoselectivity (*dr* $>$ 99:1). Generally, electron-neutral and electron-rich pyrrolidinyl benzamides **136** provided higher yields than electron-deficient substrates. Imines **137** bearing an electron-donating *p*-methyl group required the extra addition of Ag_2CO_3 for a successful reaction. Authors demonstrated that the *N*-perfluorobutanesulfinyl group could be readily removed by the treatment with HCl allowing access to highly enantiomerically enriched amine hydrochlorides. In addition, authors suggested a possible stereochemical model for the developed transformation. It was believed that this reaction proceeded through intermediate **141** with the C_4F_9 substituent pointing away from the reaction center, while rhodium is coordinatively attached to the sulfinyl group's oxygen.



Scheme 45 Rhodium-catalyzed ferrocene **132** C—H bond amination with isocyanates.

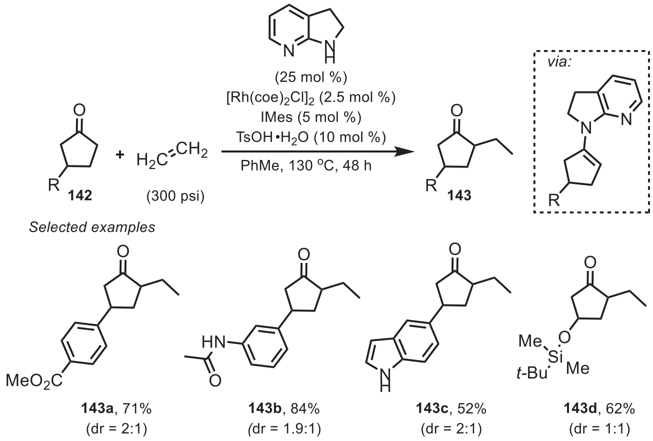


Scheme 46 Rhodium-catalyzed cyclization of benzamides **134**.

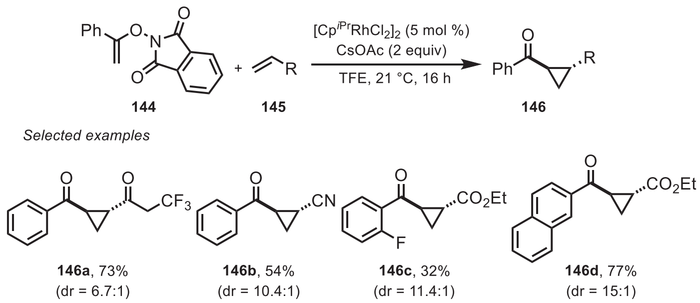


Scheme 47 Rhodium-catalyzed benzamide **136** C—H bond functionalization.

In 2014 Dong and Mo described the development of a ketone **142** α-alkylation strategy using ethylene as the alkylating agent, the reaction proceeding *via* an enamine intermediate generated from ketone **142** and catalytic amount of dihydropyrrolopyridine (Scheme 48).[93] Substrate scope was examined with a wide range of ketones **142** decorated with various functional groups, all of which were well-tolerated under the alkylation reaction conditions. Ether, carboxylic acid ester, bromoaryl, nitrile, and thioether functionalities proved to be compatible facilitating the formation of corresponding ketones **143** in yields up to 78%. Substrates containing competitive alkylation sites such as secondary amides, malonates and aliphatic esters gave chemo- and regioselective ethylation exclusively at the ketone C5 position in yields from 84% to 90%. Furthermore, reactive functional groups including free tertiary and primary alcohols, free phenols, unprotected indoles and amines reacted smoothly under optimized reaction conditions giving corresponding products **143** in moderate to high yields (52—95%). Despite the exceptionally good functional group



Scheme 48 Rhodium-catalyzed ketone **142** α-alkylation.



Scheme 49 Rhodium-catalyzed cyclopropane **146** synthesis.

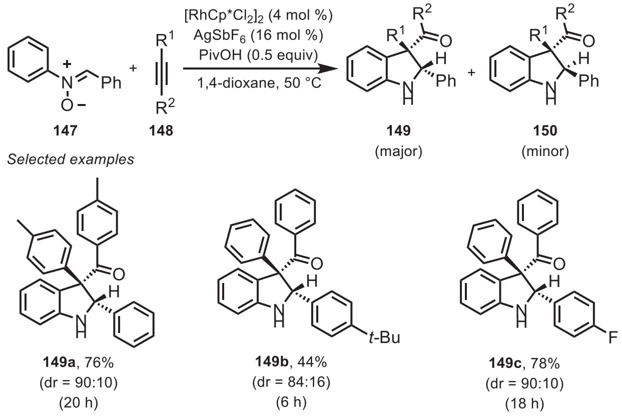
tolerance under the reaction conditions, products **143** formed only with slight excess of the diastereomeric ratio with the *cis*-diastereomer predominating.

Rh(III)-catalyzed cyclopropanation reaction between *N*-enoxyphtalimides **144** and alkenes **145** was discovered by Piou and Rovis in 2014 showing rare example on Rh(III)-catalyzed cyclopropane **146** synthesis (Scheme 49).[94] Through a careful ligand screening, a new monosubstituted *i*Pr-cyclopentadienyl ligand enabled a high degree of diastereocontrol for 1,2-disubstituted *trans*-cyclopropane **146** synthesis. Diverse substitution patterns on alkene **145** and aryl unit of the *N*-enoxyphtalimide **144** were examined, as a result, products **146** were obtained in high yields in a highly diastereoselective manner regardless of the substituent electronic or steric nature.

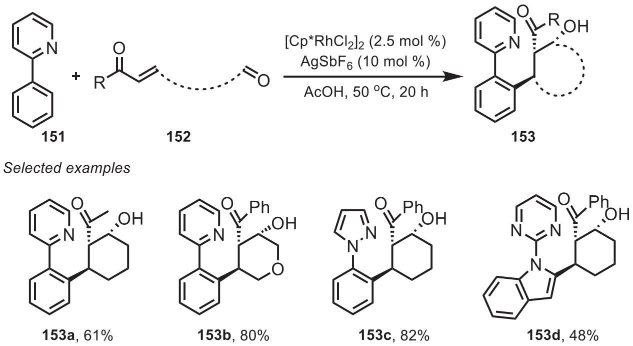
An interesting methodology for rhodium(III) catalyzed cyclization of arylnitrones **147** to indolines **149** and **150** was shown by Dateer and Chang in 2015 (Scheme 50).[95] The dual role of the Rh(III) catalyst—in the C—H bond activation and oxygen atom transfer, allowed the cyclization under mild reaction conditions giving access to indoline **149** products in good yields and moderate to high diastereoselectivity. Reactions employing arylnitrone substrates **147** bearing an electron-withdrawing group in aryl moiety proceeded highly stereoselectively. A similar level of selectivity was observed using arylnitrones with 4-*t*-Bu, 4-methoxy and 4-methyl substituents at the phenylimino moiety. It was observed that both asymmetric and symmetric alkynes yielded corresponding cyclic products in lower yields and lower diastereoselectivities than diphenylacetylene.

In 2016 Ellman and coworker developed a Rh(III)-catalyzed C—H bond addition/aldol cyclization cascade which represented the C—H bond addition across an alkene π-bond and a carbonyl (Scheme 51).[96] The reported transformation was carried out under mild conditions resulting in cyclic β-hydroxy ketones **153** with three contiguous stereocenters. Substrates with electron-donating and withdrawing substituents on phenyl moiety afforded products as single diastereomers in high yields (up to 90%). Additionally, the introduction of a heteroatom into the tether of **152** proved to be an acceptable substitution and provided corresponding heterocycle **153b**.

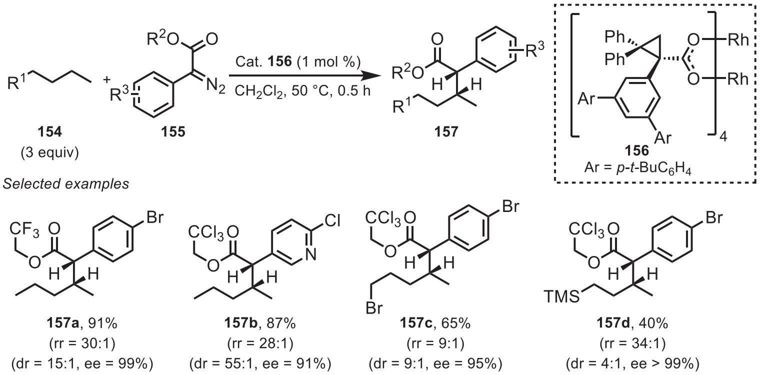
The site-selective, diastereoselective and enantioselective C—H functionalization of *n*-alkanes and terminally substituted *n*-alkyl compounds was achieved using dirhodium catalyst **156** by Davies and coworkers in 2016 (Scheme 52).[97] A new class of



Scheme 50 Rhodium-catalyzed diastereoselective nitrone **147** cyclization.



Scheme 51 Enone-tethered aldehyde **152** C—H addition/cyclization reaction.



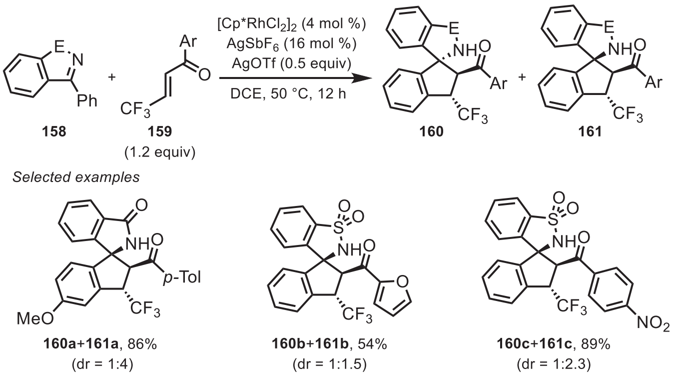
Scheme 52 Unactivated alkane **154** C—H bond functionalization.

D_2-symmetric dirhodium catalysts was developed that ensured the high site-selectivity as well as high levels of enantio- and diastereocontrol for the reported methodology. Substrate scope with respect to both reaction components—alkanes **154** and diazo compounds **155** was investigated. Authors noted that regardless of alkyl chain length, reaction remained C2 site selective. Terminal functional groups in alkanes **154**, such as halogen, TMS and ester, also gave C2 C—H functionalization products **157** with high enantioselectivity (90—99% *ee*), but variable diastereoselectivity (4:1—9:1 *dr*).

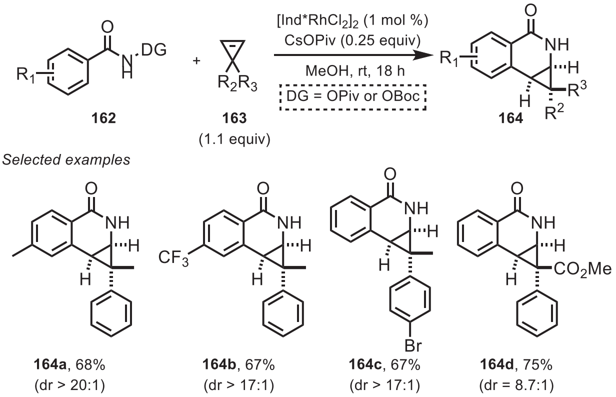
In 2017, Li and coworkers performed the Rh(III)-catalyzed [3+2] annulation reaction of cyclic *N*-sulfonyl or *N*-acyl ketimines **158** with activated alkenes **159** which led to the synthesis of spirocycles **160**/**161** with three continuous stereocenters (Scheme 53).[98] The investigation of the substrate scope revealed that an electron-donating group like methoxy in ketimine substrate **158** benefited the reaction while electron-withdrawing groups such as *p*-fluoro decreased the efficiency of developed reaction. Noteworthy, authors observed, that the diastereoselectivity can be tuned by the silver additive.

The diastereoselective coupling of *O*-substituted arylhydroxamates **162** and cyclopropenes **163** realized under Rh(III)-catalyzed conditions was successfully developed by Paton, Rovis and coworkers in 2017 (Scheme 54).[99] Initially, authors performed a ligand optimization studies and found that the heptamethylindenyl ligand ensured high diastereoselectivity in the synthesis of cyclopropa[*c*]dihydroisoquinolones **164**. Both benzamide directing groups *O*-Piv and *O*-Boc were used for investigation of the reaction scope. The *O*-Piv directing group with an electron-rich *p*-methoxy substituent gave products **164** with excellent diastereoselectivity (>20:1 *dr*) compared to electron-deficient substituents (around 10:1 *dr*). Variations of the cyclopropene coupling partners **163** were explored using unsubstituted *O*-Boc benzhydroxamate **162** and it was found that cyclopropenes bearing diverse substitution patterns underwent reaction smoothly, yielding products in moderate to good yields with very good diastereoselectivity regardless of the electronic nature of substituents.

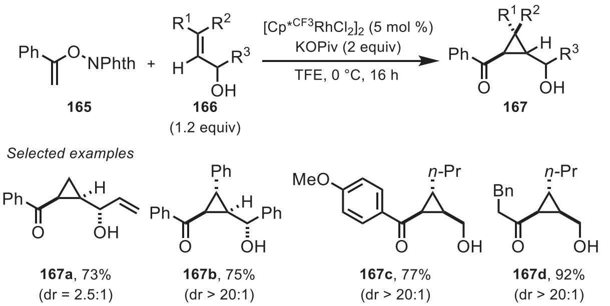
Two years later, Phipps and Rovis reported a diastereoselective [2+1] annulation reaction resulting in substituted cyclopropylketones **167** (Scheme 55).[100] Reaction was initiated by alkenyl C—H activation of *N*-enoxyphthalimides **165**. Interestingly, phthalimide group in the substrate **165** serves as a traceless directing group and as an internal oxidant. Authors proposed that the diastereoselectivity of the reaction arose from an intermediate, which forms by a ring-opening acylation of the allylic alcohol



Scheme 53 Rhodium-catalyzed cyclic imine **158** spiroannulation with alkenes **159**.



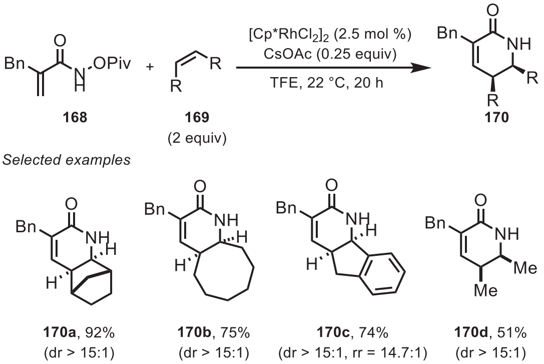
Scheme 54 Rhodium-catalyzed cyclopropene **163** benzamidation.



Scheme 55 Rhodium-catalyzed diastereoselective cyclopropanation of allylic alcohol **166**.

166. Furthermore, authors observed that the major diastereomer of trisubstituted cyclopropane product **167** directly correlated with alkene **166** double bond geometry.

In 2020, Rovis and coworkers reported a regio- and diastereospecific synthetic approach toward unprotected δ-lactams **170** from non-activated alkenes **169** and a diverse scope of acrylamides **168** (Scheme 56).[101] The optimization studies revealed that $[Cp^{*}RhCl_2]_2$ catalyst in combination with substoichiometric amount of CsOAc in TFE solvent at 22 °C were the most suitable



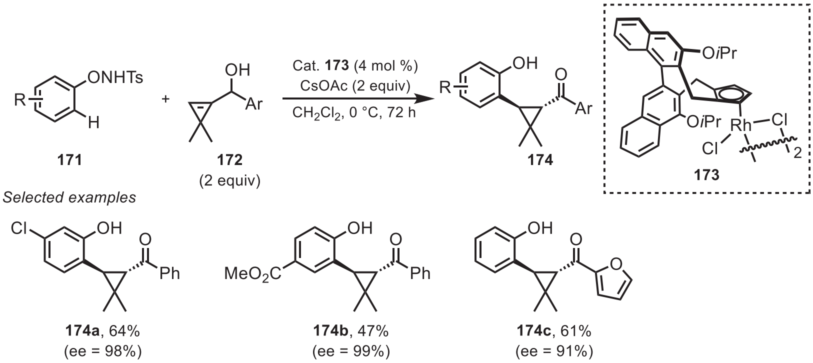
Scheme 56 Rhodium-catalyzed synthesis of unprotected δ-lactams **170**.

conditions for the stereoselective synthesis of δ-lactams **170**. The substrate scope for the diastereoselective synthesis of δ-lactams **170** was explored using several cyclic alkenes **169** delivering the desired products in medium to great yields with excellent diastereoselectivity (diastereomeric ratio higher than 13.1:1). Moreover, acyclic olefins were also competent reagents for the developed transformation, yielding lactams **170** with either *cis* or *trans* relative stereochemistry, depending on *E* or *Z* configuration of the alkene **169** double bond.

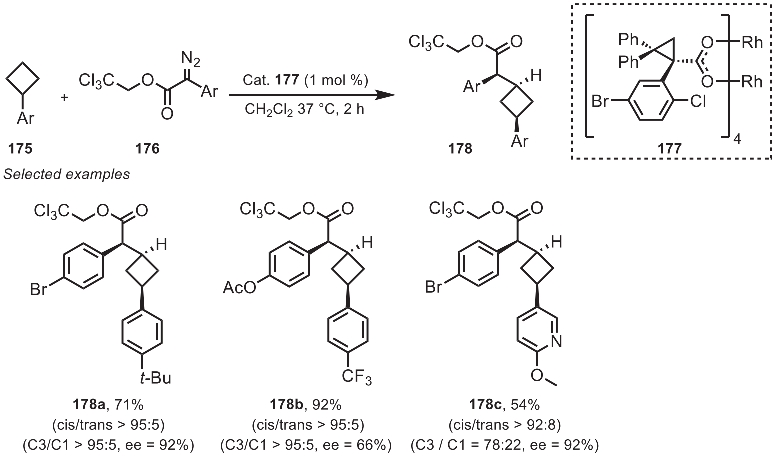
Yi, Li and coworkers reported the Rh(III)-catalyzed redox-neutral C—H cyclopropylation of *N*-phenoxysulfonamides **171** with cyclopropenyl alcohols **172** (Scheme 57).[102] The developed methodology enabled a straightforward access to functionalized *trans*-cyclopropanes **174** in a diastereo- and enantioselective manner. The reaction conditions were compatible with a broad substrate scope, tolerating electronically different *N*-phenoxytosylamides **171** substituents and a broad variety of aryl-substituted cyclopropenyl alcohols **172**. Moreover, extensive mechanistic studies by series of control experiments and DFT calculations revealed that dual directing group-assisted (OH and O-NHTs) concerted proton-hydride transfer to a Rh(V) nitrenoid determined the unique regio-, (*S*,*S*)-enantio-, and *trans*-diastereoselectivity of the cyclopropanation reaction.

Regio- and stereoselective Rh(II)-catalyzed C—H functionalization of cyclobutanes **175** with diazo compounds **176** was demonstrated in 2020 by Davies and coworkers (Scheme 58).[103] In their report, authors demonstrated that, using an appropriate catalyst, C—H functionalization of cyclobutanes **175** may occur either at C1 or at C3 position. In this context, employing a slightly modified dirhodium catalyst **177**,[97] the desired *p*-substituted cyclobutanes **178** were obtained in moderate to high yields (29—92%) with high diastereo-, enantio- and regioselectivity. Rationalizing the regioselectivity of the developed transformation, authors concluded that the reaction at C1 site is more electronically preferred due to the influence of the aryl group, at the same time, C1 is sterically hindered as a tertiary site. Thus, in order to achieve selective reaction at C3 sterically bulky catalysts were required.

In 2020, Cramer and coworker reported a useful synthetic approach toward α-alkoxylated γ-lactams **181** *via* a Rh(III)-catalyzed diastereoselective cyclopropane **179** C—H/C—C activation sequence (Scheme 59).[104] Performed optimization studies showed that combination of $[Cp^*RhCl_2]_2$ catalyst and Na_2CO_3 additive was the most suitable for the developed reaction. The transformation



Scheme 57 Rhodium-catalyzed *N*-phenoxysulfonamide **171** C—H functionalization with alcohols **172**.

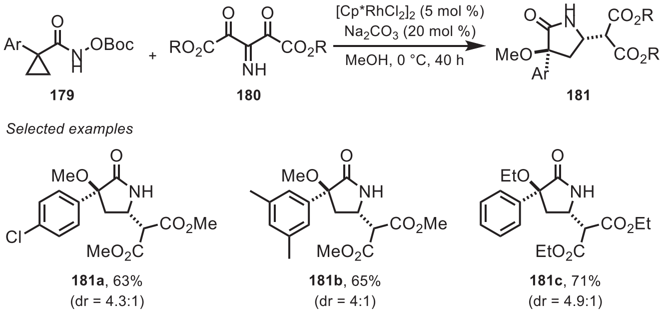


178a, 71%
(cis/trans > 95:5)
(C3/C1 > 95:5, ee = 92%)

178b, 92%
(cis/trans > 95:5)
(C3/C1 > 95:5, ee = 66%)

178c, 54%
(cis/trans > 92:8)
(C3 / C1 = 78:22, ee = 92%)

Scheme 58 Regio- and stereospecific Rh(II)-catalyzed C—H functionalization of cyclobutanes **175**.



181a, 63%
(dr = 4.3:1)

181b, 65%
(dr = 4:1)

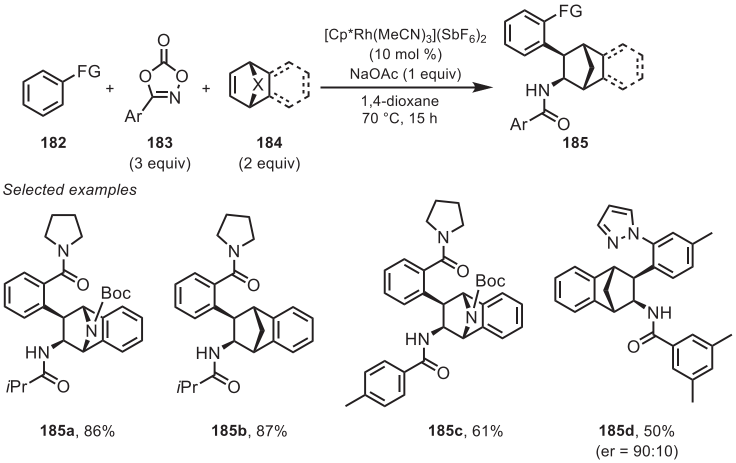
181c, 71%
(dr = 4.9:1)

Scheme 59 Rhodium-catalyzed synthesis of α-alkoxylated γ-lactams **181**.

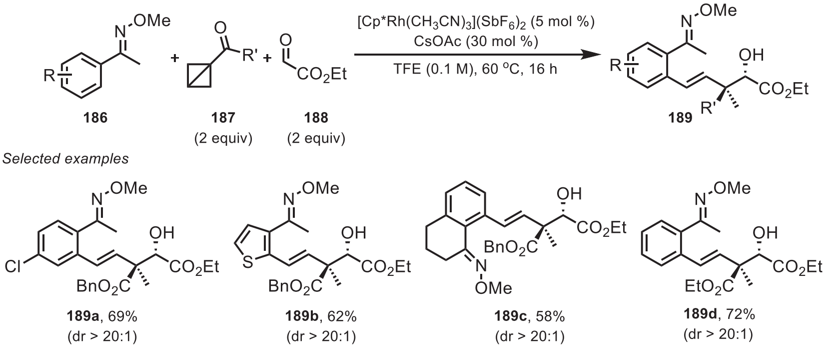
proceeded successfully for a wide range of substituted aryl cyclopropanes **179** bearing an electron-donating group, delivering access to products **181** in generally good yields (up to 71%) and with relatively good *trans*-selectivity (diastereomeric ratio up to 6.7:1). On the other hand, substrates **179**, where aryl substituents contained electron-withdrawing group such as trifluoromethyl or nitro group, presented lower reactivity, and the corresponding products **181** were obtained with yields <40%. Additionally, authors demonstrated that the aryl functionality was crucial for a successful transformation, as benzylcyclopropane yielded γ-lactam in only 8% yield.

As experts in transition metal catalyzed three-component coupling reactions, Ellman and coworkers reported in 2021 an efficient rhodium-catalyzed synthesis of a bridged bicycles **185** (Scheme 60).[105] As a result from the optimization studies, authors found that the optimal results could be achieved using cationic Rh(III) catalyst $[Cp^*Rh(MeCN)_3](SbF_6)_2$ in combination with NaOAc additive. Besides, authors ascertained that cobalt, iridium or ruthenium catalysts failed to give the desired product. A variety of [2.2.1]-bridged bicycles **184** with oxygen, nitrogen and carbon at the bridge position were evaluated. Tertiary and secondary amides, pyrazole, and triazole as substituents in aryl compound **182** were found to be effective directing groups for this transformation. In general, varying the substitution patterns on each of the three reaction components (aryl compound **182**, dioxazolone **183** and alkene **184**), the corresponding products **185** were obtained in very good yields (up to 91%) as single diastereomers. Additionally, authors were able to perform asymmetric version of the developed reaction, using Rh(III) complex in combination with chiral ligand previously developed by Cramer[106] to obtain enantiopure products **185** with enantiomeric ratio up to 92:8.

At the same time, Glorius and his research group demonstrated a diastereoselective construction of quaternary carbon centers starting from oxime ethers **186**, strained bicyclobutanes **187**, and ethyl glyoxylate **188** (Scheme 61).[107] A three-component coupling was realized using the cationic Rh catalyst $[Cp^*Rh(MeCN)_3](SbF_6)_2$ in combination with CsOAc additive in TFE solvent at 60 °C. Impressively, during the substrate scope investigation, alcohols **189** were obtained in excellent diastereoselectivity (*dr* >



Scheme 60 Rhodium-catalyzed synthesis od bridged bicycles **185**.



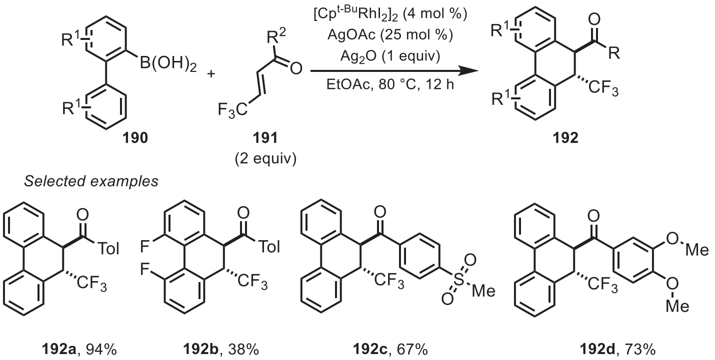
Scheme 61 Rhodium-catalyzed three-component coupling.

20:1 in all cases), exclusively as *E* double bond isomers. However, yields of isolated products **189** were moderate to very good, ranging from 44% to 81%. Authors found that alkyl and aryl aldehydes were not tolerated under the optimized reaction conditions, producing only trace amounts of the desired products. Nevertheless, it was demonstrated, that the developed transformation may be easily scaled up without significant loss of product yield.

A rhodium-catalyzed annulation of 2-biphenylboronic acid derivatives **190** with activated alkenes **191** was demonstrated by Liu, Chang, Li and coworkers in 2021 (Scheme 62).[108] Using a rhodium catalyst in combination with silver acetate and silver oxide additives, the corresponding trifluoromethyl group containing tricycles **192** were obtained in moderate to excellent yields (up to 99%) predominantly as *anti*-isomers. The *anti*-geometry and regioselectivity of the products **192** had been unambiguously confirmed by X-ray diffraction analysis. Additionally, authors demonstrated that instead of trifluoromethyl alkenes **191**, cyclopropenones and other activated alkenes could be employed as coupling partners, leading to formation of synthetically useful fused cyclic products.

Palladium

In general, palladium is one of the most exploited transition metals in catalysis. Particular attention is devoted to the use of palladium catalysts for C(sp^2)-H and C(sp^3)-H bond activation. Unlike other transition metals, palladium participates in cyclometalation with a wide variety of directing groups thus allowing to achieve excellent site selectivity for C—H functionalization of arene



Scheme 62 Rhodium-catalyzed annulation of boronic acid **190** with activated alkenes **191**.

ortho-, *meta-*, and even *para*-position. Efficient C–H bond functionalization methodology under palladium catalysis has been discovered that allows access to various natural products, including alkaloids, biologically active compounds, agrochemicals, polymers, etc.[2,3,109–112]

Palladium catalyzed asymmetric C–H bond functionalizations, including diastereoselective and enantioselective transformations, are well-studied over the last decades. In recent years, several general review articles and book chapters are published and successfully cover the key contributions in this field. Therefore, palladium-catalyzed diastereoselective C–H bond functionalization will not be analyzed in this chapter.[113–118]

Silver

If compared to other second-row transition metals silver is much less expensive. Because of Ag(I) unique d^{10} electronic configuration, it easily coordinates with various π-donors, like C=Y and C≡Y bonds (Y = C or heteroatom) and n-donors, for example, amines, phosphines and ethers. Among other transition metal catalysis, silver catalyzed C–H bond functionalization reactions has emerged as a powerful method.[119–122] Despite the applicability of Ag(I) for C(sp^2)-H and C(sp^3)-H bond functionalization reactions as well as enantioselective C–H functionalization of alkenes and alkynes, the diastereoselective C–H bond functionalizations using silver salts still remain underdeveloped.

Third Row Transition Metals

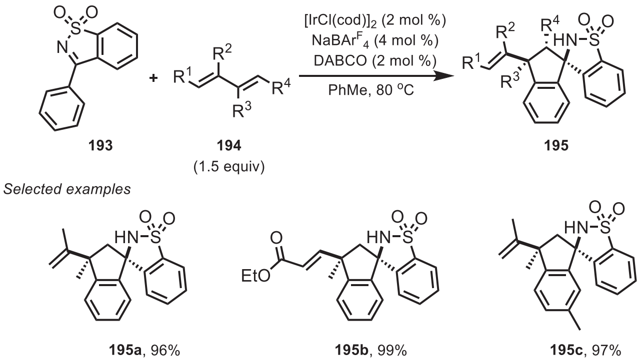
Third row transition metals, specifically Pt and Au are the most expensive from all. Despite that, similar to second-row transition metals, third row transition metals (Ir, Pt, Au) have been extensively used for C–H bond activation and functionalization reactions. For a long time without appropriate alternatives they have been exploited for hydrofunctionalization reactions.[123]

Iridium

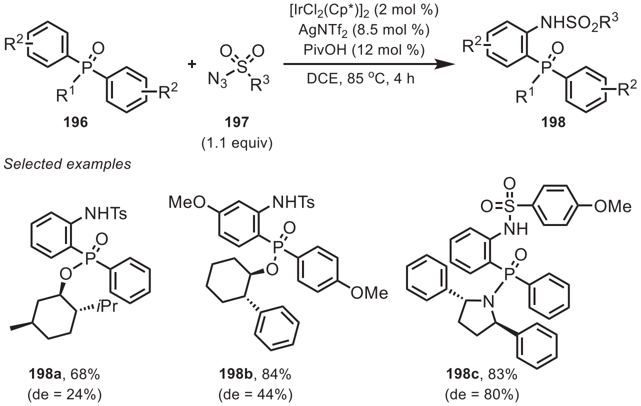
Iridium is one the most important element of the platinum group elements having the widest range of oxidation states i.e., −3 to +9 among all of the transition metals. Iridium complexes present various unique properties that explore a broad area of applications in organic synthesis, materials science and medicinal chemistry. Iridium has the ability to promote a wide range of reactions including C–H bond activation, cross-coupling, hydrogenation and carbonylation. Despite their many advantages, iridium catalysts are still relatively expensive and less abundant compared to other transition metals. However, advances in iridium catalysis have led to the development of more efficient and cost-effective catalysts, making iridium catalysis a promising area of research for future chemical transformations.[124–126] Herein we will overview several interesting examples for diastereoselective C–H bond functionalization under iridium catalysis.

In 2013, Nishimura and coworkers described the iridium-catalyzed [3+2] annulation of cyclic *N*-sulfonyl ketimines **193** with 1,3-dienes **194**, which resulted in the formation of aminoindane derivatives **195** in high yields and with high diastereoselectivity (Scheme 63).[127] The reactions were performed using various 1,3-dienes **194** and cyclic *N*-sulfonyl ketimines **193** with *para*- and *meta*-substituted phenyl groups. It was observed, that dienes underwent the reaction at the more substituted double bond site in highly regioselective manner. Noteworthy, electron-deficient dienes—substituted with sulfonyl or carbonyl groups were also competent reactants toward presented annulation. In this case reaction occurred at the more electron-rich double bond. In the same year, authors developed an enantioselective version of the developed reaction.[128]

In 2014, Park, Chang and coworkers described a novel methodology for the direct C–H amidation of arylphosphoryl compounds **196** using a Cp*Ir(III) catalytic system under relatively mild conditions (Scheme 64).[129] The reported procedure was compatible with various functional groups, such as alkyl, alkoxy, protected amines and halogen atoms and it has been



Scheme 63 Iridium catalyzed annulation of cyclic *N*-sulfonyl ketimines **193** with 1,3-dienes **194**.

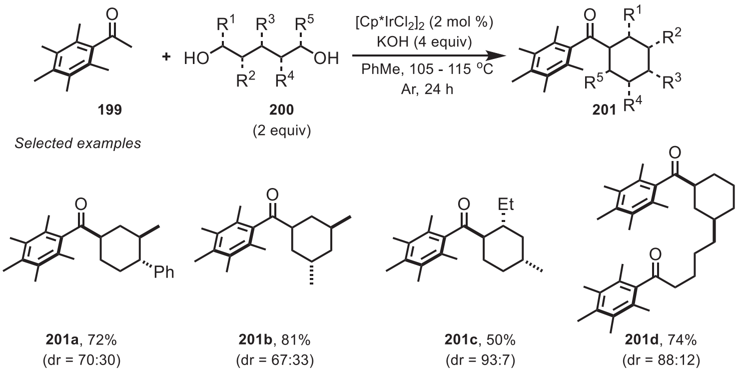


Scheme 64 Iridium-catalyzed C—H amidation of arylphosphoryls **196**.

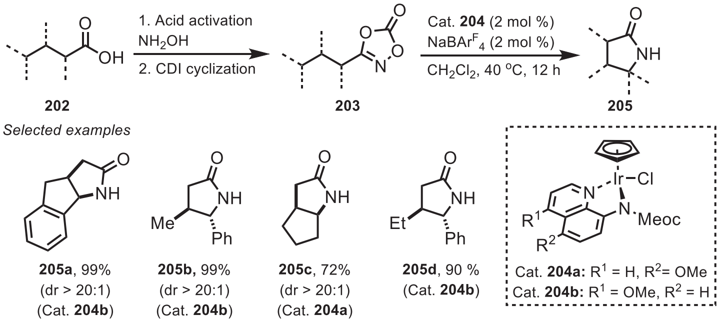
successfully applied for the asymmetric reaction giving rise to compounds with a P-chirality with a diastereomeric ratio up to 19:1. The authors explored a stereoselective C—H amidation by using diarylphosphorus compounds **196** possessing chiral auxiliaries. The best results were obtained using C_2-symmetric chiral pyrrolidine auxiliary (example **198c**).

Donohoe and coworkers in 2018 had developed an iridium-catalyzed methodology for the synthesis of functionalized cyclohexanes **201** using methyl ketones **199** and 1,5-diols **200** (Scheme 65).[130] The process utilizes two sequential hydrogen borrowing sequences, creating access to multisubstituted cyclic products **201** with high levels of stereocontrol. Developed transformation was applied to a broad range of diols **200**, including those with electron-donating, electron-deficient, halogen-containing, and sterically encumbered groups. Interestingly, rationalization of the reaction stereochemical outcome led authors to conclude that stereoselectivity at each position is controlled by different factors. In this context, stereochemistry at C1 is set under thermodynamic control by base-mediated epimerization, C2 is dictated by the facial selectivity of attack on a cyclic enone intermediate by iridium hydride, C3 can epimerize after oxidation to the aldehyde and C4 is translated from the diol **200** starting material with complete fidelity.

Iridium catalyzed transformation of 1,4,2-dioxazol-5-ones **203** into corresponding γ-lactams **205** was reported by Baik, Chang and coworkers in the same year (Scheme 66).[131] One of the major advantages of the reported protocol was the substrate accessibility. Respectively, various 1,4,2-dioxazol-5-ones **203** were obtained from carboxylic acids *via* two steps sequence of acid activation followed by carbonylative cyclization, both of which are highly effective and substrates were prepared in excellent yields. Functionalization of a secondary benzylic C—H bond in the cyclopentyl ring resulted in *cis*-tricyclic γ-lactam **205a** as a sole product in 99% yield. In the case of non-equivalent γ and γ′ C—H bonds, benzylic C—H bonds were favored over non-activated secondary C—H



Scheme 65 Iridium-catalyzed synthesis of functionalized cyclohexanes **201**.



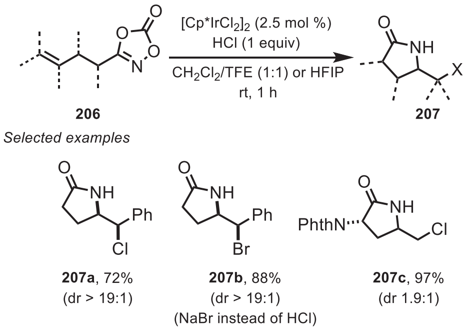
Scheme 66 Iridium catalyzed transformation from carboxylic acids **202** to γ-lactams **205**.

bonds (product **205b**). Moreover, the amidation protocol was also highly effective toward more complex molecules that possessed multiple reactive C—H bonds.

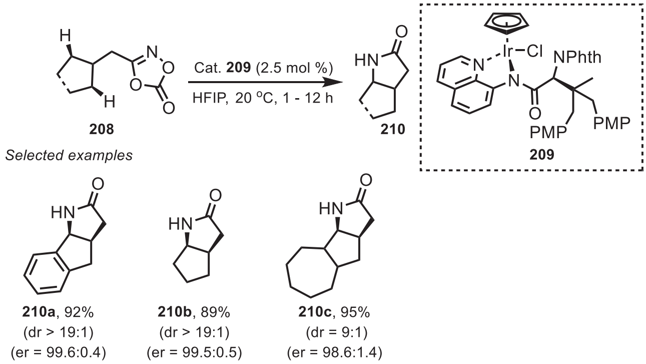
A year later, stereodefined access to γ-lactams **207** *via* iridium-catalyzed olefin **206** difunctionalization was developed by Chang and Hong (Scheme 67).[132] Substituted dioxazolone containing olefins **206** underwent haloamidation reaction under mild conditions by using HCl and NaCl/NaBr as the halogen source. Reactions with various dioxazolones **206** bearing aryl- and alkyl substituents were carried out resulting in high yields and generally great diastereoselectivity. The effect of the double bond configuration on the stereochemistry of the products was demonstrated by subjecting both *E*/*Z* isomers to the reaction conditions. It was found, that dioxazolones **206** bearing *E*-configuration of the double bond gave *threo*-lactams **207**, but dioxazolones **206** bearing *Z*-alkenyl groups yielded *erythro*-lactams **207**.

A newly designed α-amino-acid-based chiral ligand was used by Chang, He, Chen and coworkers in 2019 for enantioselective Ir(III)-catalyzed intramolecular dioxazolone **208** amidation (Scheme 68).[133] This reaction proceeded with excellent efficiency and outstanding enantioselectivity for both activated and non-activated C(sp^3)-H bonds under very mild conditions where a broad scope of substituted benzylic, allylic and alkyl substrates were tolerated. In addition to enantioselective methylene group C—H bond amidation, desymmetrization of substrates containing two symmetric methylene groups worked well to form more complex γ-lactams carrying consecutive stereogenic centers. Despite that, only a few examples were represented for a diastereoselective C—H amidation of dioxozolones **208**.

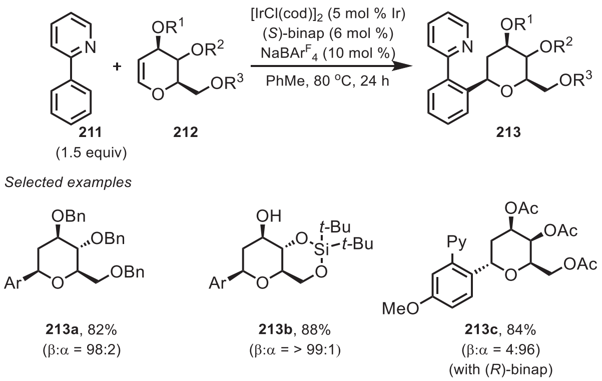
In the same year, Nishimura and coworkers developed a novel method for the regio- and diastereoselective hydroarylation of chiral glycals **212** with aromatic compounds **211** using an iridium-catalyzed system containing of [IrCl(cod)]$_2$, chiral phosphine ligand and NaBAr$^F{}_4$ (Scheme 69).[134] The reaction occurred *via ortho*-C-H activation of an aromatic ring followed by regio- and stereoselective addition to glycals **212** giving hydroarylation products **213** in high yields and selectivity. In addition, authors demonstrated that the stereoselectivity of the addition reaction can be controlled by the choice of ligand resulting in α- or β-selective hydroarylation products **213**.



Scheme 67 Iridium-catalyzed olefin **206** difunctionalization by haloamidation.

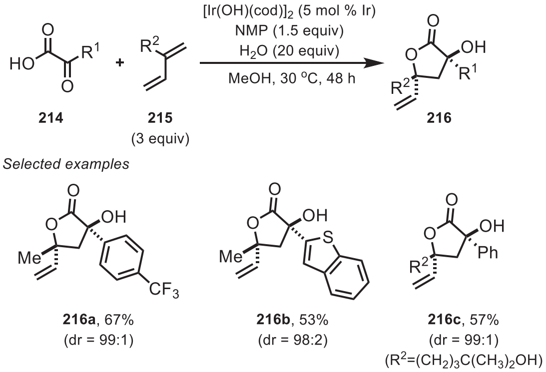


Scheme 68 Intramolecular dioxazolone **208** amidation employing amino-acid-based Ir catalyst **209**.



Scheme 69 Iridium-catalyzed diastereoselective hydroarylation of chiral glycals **212**.

In 2021, Nishimura and coworkers reported a stereoselective [3+2] annulation of various α-oxocarboxylic acids **214** with 1,3-dienes **215** under iridium catalysis yielding corresponding α-hydroxy-β-lactones **216** in good yields and high degree of selectivity for 3,5-*trans* relative stereochemistry (Scheme 70).[135] Substrate scope was explored with a variety of aryl-substituted α-oxocarboxylic acids **214**. In contrast to *m*-substituted phenyl groups, *o*-methyl-substituted substrate reaction was slow and produced the corresponding lactone in low yield (24%). Alkyl-substituted α-oxocarboxylic acids **214**, such as pyruvic acid, 2-oxobutyric acid,



Scheme 70 Stereoselective annulation of α-oxocarboxylic acids **214** with 1,3-dienes **215**.

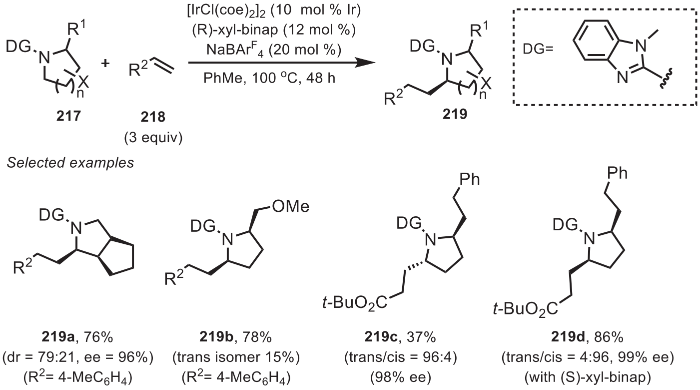
2-oxododecanoic acid, and 2-cyclohexyl-2-oxoacetic acid also participated in the annulation reaction and gave products in moderate to good yields (20—65%) with high diastereoselectivity (99:1).

Recently, in 2022, Nishimura and coworkers reported a reaction of pyrrolidine **217** derivatives with various terminal alkenes **218** using cationic iridium/chiral diphosphine catalyst in order to obtain α-alkylated products **219** (Scheme 71).[136] In their report, *N*-methylbenzimidazole was used as a directing group to perform enantio- and diastereoselective α-C(sp^3)-H alkylation producing pyrrolidines **219** in high yields and excellent enantio-and diastereoselectivity. The ring size of the cyclic amines significantly changed the reactivity; respectively the reaction of four-membered azetizine was quite slow, whereas six- and seven-membered piperidine and azepane analogs reacted smoothly. The use of (*R*)-xyl-binap as a ligand for the reaction with *t*-Bu acrylate resulted in *trans*-isomer as the major product (*trans*:*cis* = 96:4) while the same reaction using the (*S*)-xyl-binap ligand gave *cis*-isomer as the major product (*trans*:*cis* = 4:96). Developed catalytic system was successfully applied for further developments by Nishimura and coworkers.[137,138]

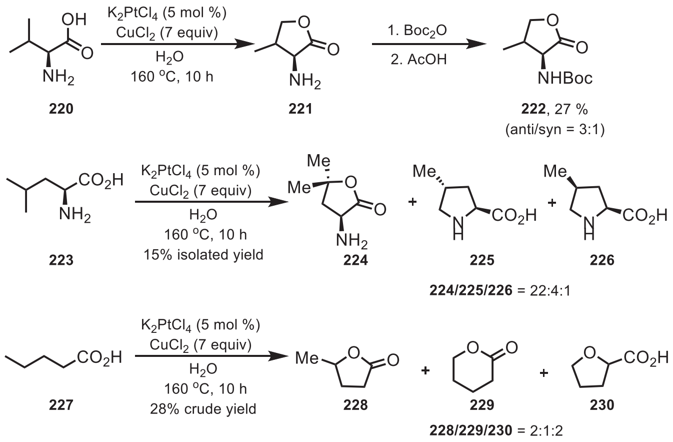
Platinum

Platinum has played a central role in the evolution of C—H activation chemistry by soluble species over the last half century, in both fundamental understanding and approaches to actual functionalization. A number of early examples of intramolecular C—H activation—ligand cyclometalation—involved Pt complexes. More recently, however, with the pronounced turn to the cheaper earth-abundant first row transition metals, the prevalence of Pt in C—H activation reports appears to have fallen off significantly.[139]

In 2001, Sames and coworkers reported a methodology on amino acid selective functionalization, using K_2PtCl_4 catalyst and superstoichiometric amount of $CuCl_2$ (Scheme 72).[140] In their report, L-Valine provided a 3:1 *syn*/*anti* mixture of Boc-protected lactone **222** in 27% yield. Unfortunately, L-Leucine **223** and other tested amino acids yielded products as a mixture of the corresponding lactone **224** and lactams **225** and **226** in different rations. Additionally, valeric acid **227** was also tested and gave a mixture



Scheme 71 Enantioselective alkylation of pyrrolidines **217** using Ir catalyst with chiral ligands.



Scheme 72 Platinum-catalyzed C—H functionalization of amino acids **220, 223** and valeric acid **227**.

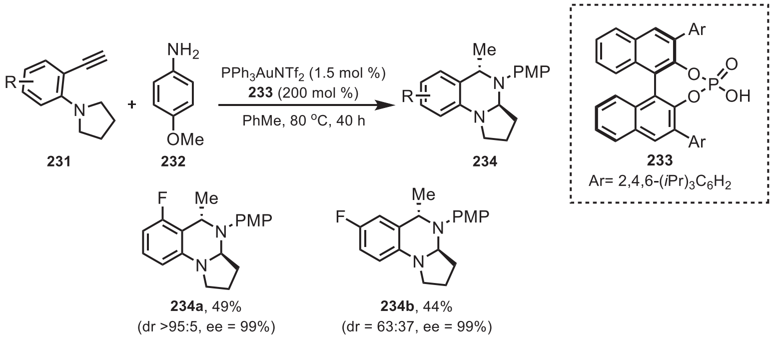
of regioisomers 228—230. Expectedly, L-Proline did not participate in this transformation. Despite the low yields of products, a diastereoselective straightforward construction of a complex heterocycles starting from simple amino acids is crucial in the field of organic synthesis.

Gold

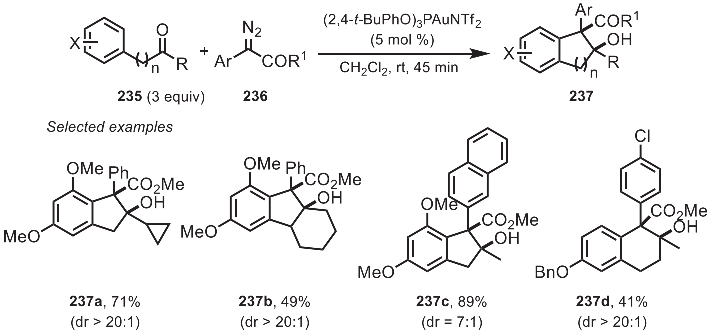
The first decade of the 21st century witnessed a "gold rush" in homogeneous gold catalysis where new reaction modes and novel reactivities were uncovered, together with the discovery of numerous ligands and gold catalysts.[141—144] The significance of gold catalysis has been approved by the numerous applications in several fields, such as asymmetric synthesis, total synthesis of complex natural products, and C—H bond functionalization. Herein we will overview some important examples on diastereoselective C—H bond functionalization using gold catalysis.

In 2013, Gong and coworkers developed a combined gold/Brønsted acid catalyzed hydroamination/redox reaction cascade for the synthesis of cyclic aminals **234** (Scheme 73).[145] In their report, the following catalytic system was used: Au catalyst and CF_3SO_3H at elevated temperature in toluene. A broad scope of terminal acetylenes **231** was examined under the optimized reaction conditions in combination with a variety of anilines **232**, delivering 24 different aminals **234** in yields ranging from 71% to 99%. Despite that, the diastereomeric ratio of the products was generally mediocre. As a proof of concept, authors investigated enantioselective version of the developed transformation by performing additional optimization. As a result, the use of PPh_3AuNTf_2 catalyst and chiral BINOL-derived phosphoric acid **233** ensured the excellent diastereoselectivity (up to 19:1 *dr*) and enantiopurity (99% *ee*) of the obtained product, albeit the yield was significantly lower even at the prolonged reaction time.

Three years later, in 2016, gold-catalyzed C—H bond functionalization and aldol annulation sequence was developed by Liu, Zhang and coworkers to enable the diastereoselective construction of bicyclic products **237** (Scheme 74).[146] Optimization of



Scheme 73 Cyclic aminal **234** synthesis via Au-catalyzed hydroamination.

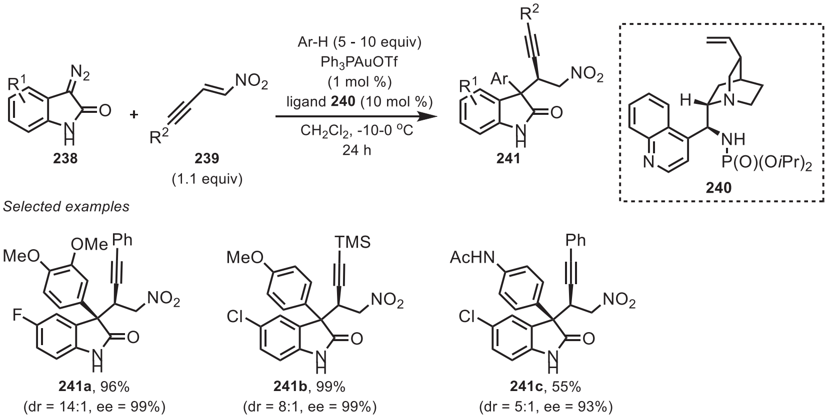


Scheme 74 Gold-catalyzed synthesis of bicyclic products **237**.

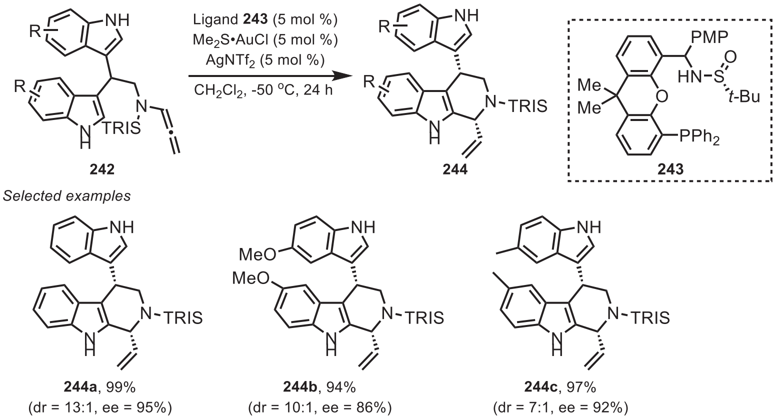
the reaction of benzyl ketone **235** with diazocompounds **236** revealed that the highest yield and diastereoselectivity in product **237** could be achieved using 5 mol% (2,4-*t*-BuPhO)$_3$PAuNTf$_2$ catalyst in dichloromethane. A variety of ketones **235** bearing an electron-donating groups in the aryl moiety were well-tolerated and smoothly participated in the reaction with a diverse scope of diazo compounds **236**, yielding 40 different bicyclic tertiary alcohols **237** in medium to good yields and with generally great diastereoselectivity.

At the same time, Zhou and coworkers reported a sequential Au(I)/chiral tertiary amine **240** catalyzed highly enantio- and diastereo-selective synthesis of quaternary oxindoles **241** from diazooxindoles **238**, enynes **239** and anisoles or thiophenes (Ar-H) (Scheme 75).[147] During optimization studies, DCM was found as the most suitable solvent for Au-catalyzed C–H functionalization reaction, while previously developed cinchonidine-based phosphoramide **240** was suitable for Michael addition of nitroenyne **239**. Halogen and alkyl functionalities as the substituents on the benzene in *meta*- and *para*-positions along with alkyl, aryl or TMS substitution patterns on enyne **239** reacted well under the reaction conditions forming 16 diverse pyrrolidinones **241** in medium to excellent yields and with great enantioselectivity. Although in some cases, especially using anisole or thiophene as aryl coupling partners, the diastereoselectivity significantly dropped.

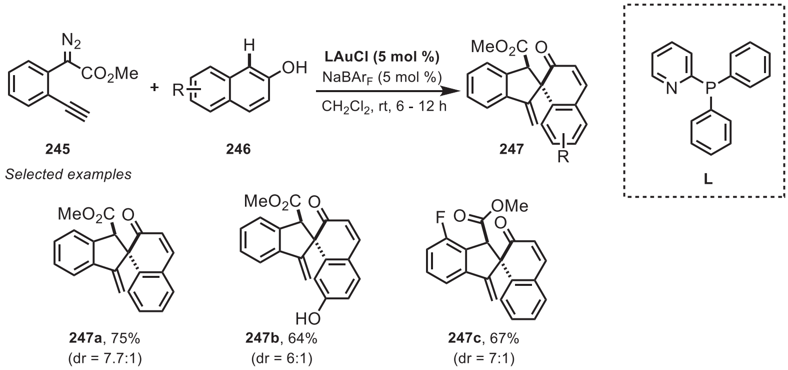
A gold-catalyzed asymmetric intramolecular cyclization of *N*-allenamides **242** was reported in 2017 by Zhang's group (Scheme 76).[148] Importantly, the resulting substituted indoles **244** are core motifs in ubiquitous biologically active alkaloids. The developed catalyst system was applied to desymmetrizative cyclization of *N*-allenamides **242** and to authors delight the corresponding products **244** were obtained in high yields (up to 99%). Moreover, these reactions were found to be not only highly enantioselective with *ee* up to 95%, but also highly diastereoselective, yielding products **244** with up to 22:1 diastereomeric ratio.



Scheme 75 Gold-catalyzed diastereoselective synthesis of quaternary oxindoles **241**.



Scheme 76 Au-catalyzed intramolecular cyclization of *N*-allenamide **242**.



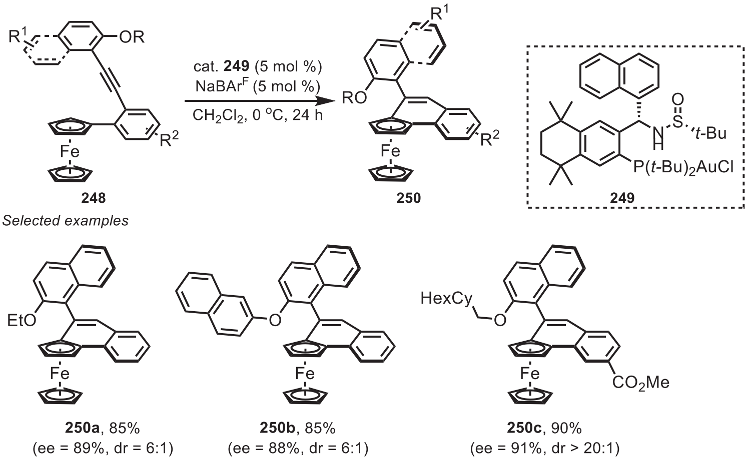
Scheme 77 Diazoacetate **245** and naphthol **246** intermolecular [4+1] spiroannulation.

A few years later, in 2020, Zhang, Liu and coworkers demonstrated a gold-catalyzed intermolecular [4+1] spiroannulation reaction between diazoacetates **245** and naphthols **246** by site-selective C–H functionalization/dearomatization sequence (Scheme 77).[149] Conceptually simple and easy to scale-up Au(I)-catalyzed reaction was found to be highly diastereoselective when LAuCl in combination with NaBAr$_F$ was employed. The reaction conditions were mild and provided products **247** in generally good yields, tolerating a wide range of substituents in naphthalene moiety and a variety of diazoesters **245** while maintaining generally good diastereoselectivity (up to 8.1:1 *dr*).

In 2021 Zhang and coworkers demonstrated simultaneous construction of axial and planar chiralities *via* the gold-catalyzed asymmetric intramolecular hydroarylation of *o*-alkynylferrocene derivatives **248** (Scheme 78).[150] The cyclohexylmethyl ether as a substituent at C2 position of naphthalene moiety was found to be crucial to achieve high enantio- and diastereoselectivity of product **250c**. Other ethers were less effective (**250a** and **250b**).

Conclusions

Increasing interest in transition metal catalyzed C–H bond activation and functionalization approach drives the scientists to -extensively investigate and discover novel methods successfully overcoming current challenges. To date, a large variety of new methodologies have been designed toward selective C–H bond functionalization including chemo-, regio-, enantio- and diastereo-selectivity. Enantioselective transformations have been achieved even with abundant first-row transition metals.



Scheme 78 Gold-catalyzed *o*-alkynylferrocene **248** intramolecular hydroarylation.

In most cases reaction diastereoselectivity is controlled by existing chiral center in substrate or directing group, or by the use of conformationally restricted cyclic substrates, whereas for enantioselective reactions—by the use of chiral catalyst. Nevertheless, the discovery of novel synthetic methods toward the diastereoselective C—H functionalizations is of great desire.

Acknowledgments

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Indole Synthesis by Cobalt-Catalyzed Intramolecular Amidation via the Oxidatively Induced Reductive Elimination Pathway

Aleksandrs Cizikovs, Emils E. Basens, Paula A. Zagorska, Artis Kinens, and Liene Grigorjeva*

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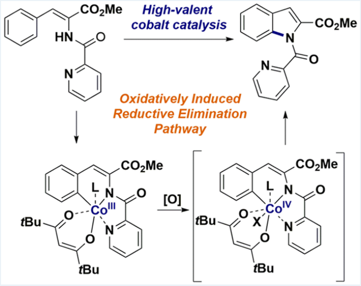
ABSTRACT: C−H bond activation and functionalization using high-valent cobalt catalysis typically involves a Co(III)/Co(I) catalytic cycle. Because of the lack of evidence and challenges associated with the high reactivity and instability of Co(IV) intermediates, reports on the C−H functionalization mechanism investigation involving Co(IV) intermediacy are still underexplored. Herein, we report an efficient synthesis of indole-2-carboxylic esters via intramolecular amidation of α-amidoacrylates and experimental and computational studies of the reaction mechanism, which involves oxidatively induced reductive elimination from Co(IV) species.



KEYWORDS: *oxidatively induced reductive elimination, cobalt, C−H functionalization, intramolecular amidation, indoles*

■ INTRODUCTION

C−H bond functionalization methodology using high-valent cobalt catalysis recently has emerged as a highly efficient and selective tool for the construction of a wide range of valuable compounds.[1−3] High-valent cobalt catalysis can be divided into two main strategies depending on the catalyst used: (1) Cp*Co(III) complexes[1a] and (2) simple Co(II) salts under oxidative conditions, typically in combination with bidentate directing group assistance.[1b] Over the past decade, more than 300 cobalt-catalyzed C−H bond functionalization reactions have been developed, and methodology has experienced very important advancements, such as directing group development (employment of traceless, transient, and native directing groups), successful examples of C(sp^3)−H bond functionalization, multicomponent addition to C−H bonds, enantioselective transformations, as well as cobalt electrocatalysis.[4] Furthermore, evidence collected over the years from mechanistic experiments and isolated intermediate species gave insight into the general operative C−H functionalization mechanism, which suggested the Co(III)/Co(I) or Co(II)/Co(III)/Co(I) catalytic cycle for the major part of the developed transformations.[2d,i,5] Although a catalytic cycle involving Co(IV) species has been considered in several cases,[6] so far only a few reports in the literature have contained detailed indisputable evidence of the involvement of Co(IV) species in C−H bond functionalization under high-valent cobalt catalysis. In 2020, the Ackermann group published a detailed mechanism investigation demonstrating experimental and computational evidence of Co(IV) species for cobaltaelectro-catalyzed C−O bond formation.[7a] A year later, in 2021, the Pérez-Temprano group reported evidence of involvement of Cp*Co(IV) species in C−S nucleophilic coupling under high-valent Cp*Co(III) catalysis.[7b] In 2023, Shi and co-workers reported base-promoted cobalt-catalyzed enantioselective C−H oxygenation involving Co(IV) species.[7c]

In 2015, Li and Ge et al. reported cobalt-catalyzed, aminoquinoline-directed intramolecular amidation of propanamides yielding lactams.[4h]

Herein, we report an experimental and computational mechanism study for a novel intramolecular C−H amidation reaction under oxidative conditions using Co(II) catalyst in combination with picolinamide chelation assistance yielding indole derivatives **2** (Figure 1).

The indole moiety is a common fragment present in various biologically active natural compounds and important pharmaceuticals.[8] The indole-2-carboxylic acid substructure with a variety of substitution patterns is an important building block for the synthesis of various biologically active compounds and FDA-approved drugs (Figure 2),[9] including, for example, atevirdine and delavirdine (used in HIV treatment),[9a,b] tubulin inhibitor D64131 (potential chemotherapy drug),[9c] and indole-2-carboxamides (potential antitubercular agents).[9d]

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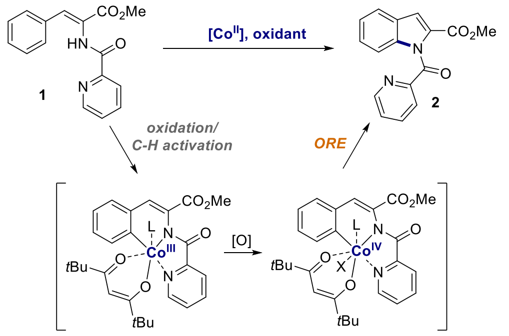


Figure 1. Indole-2 synthesis via cobalt-catalyzed intramolecular amidation.

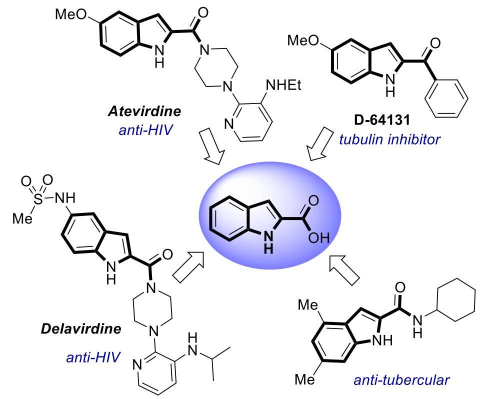


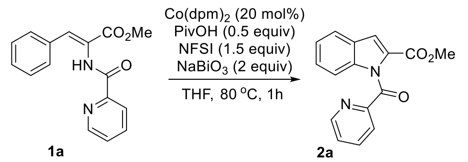
Figure 2. Examples of biologically active indole-2-carboxylic acid derivatives.

Therefore, the development of novel methodologies for indole-2-carboxylic acid synthesis is of great interest.

■ RESULTS AND DISCUSSION

Reaction Optimization Studies. We started our study with the optimization of intramolecular amidation conditions using amidoacrylate **1a**. During the optimization studies, a range of base/acid additives, cobalt salts, oxidants, and reaction solvents were evaluated (Table 1). Using commercially available Co(dpm)$_2$ catalyst in combination with *N*-fluorobenzenesulfonimide (NFSI) and $NaBiO_3$ oxidants and PivOH additive in THF at 80 °C, we observed the fast formation of indole-2-carboxylic ester **2a** in 46% yield (Table 1, entry 1). Screening of acid/base additives [see the Supporting Information (SI) for full optimization studies] and PivOH amount (entry 2) did not improve the product **2a** yield. Oxidant screening revealed that the combination of NFSI and $NaBiO_3$ works the best (entries 3–5). Interestingly, Co(OAc)$_2$, $CoCl_2$, nor Co(acac)$_2$ gave the desired product **2a** in decent yield (entries 6–8). However, the indole **2a** yield was greatly improved (77%) by exploiting in situ prepared Co(dpm)$_2$ using $CoCl_2$ and the dipivaloylmethane ligand (entry 9). Reaction solvent screening allowed the switching of the reaction solvent to a greener alternative 2-MeTHF by only slightly affecting the indole **2a** yield (entries 10–11). We found that 2 equiv of $NaBiO_3$ oxidant are necessary for a successful reaction as a reduction to 1.2 equiv decreased the indole **2a** yield to 52% (entry 12). However, a reduction in the amount of NFSI oxidant and dipivaloylmethane ligand improved the product yield (entries 13–14). As a result, optimal conditions were found, which yielded indole **2a** in 92% yield (entry 15). Besides, it is worth mentioning that in the control experiment without a cobalt catalyst (entry 16) or both oxidants (entry 18), the formation of indole **2a** was not observed. When 3.5 equiv of $NaBiO_3$ was used without NFSI (entry 17), only 9% of indole **2a** was obtained, thereby suggesting that the main role of $NaBiO_3$ is most likely the oxidation of Co(II) to Co(III).

Table 1. Optimization of Reaction Conditions[a]

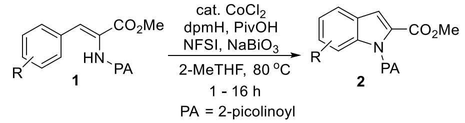


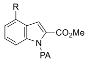
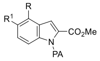
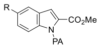
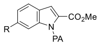
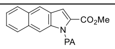
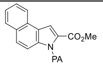
entry	change from the above conditions	yield, %[b]
1	none	46
2	PivOH (2 equiv)	36
3	$Mn(OAc)_3 \cdot 2H_2O$ instead of $NaBiO_3$	23
4	AgOAc instead of $NaBiO_3$	44
5	without $NaBiO_3$	18
6	Co(OAc)$_2$ instead of Co(dpm)$_2$	0
7	$CoCl_2$ instead of Co(dpm)$_2$	0
8	Co(acac)$_2$ instead of Co(dpm)$_2$	<5
9	$CoCl_2$, dpmH instead of Co(dpm)$_2$	77
10[c]	2-MeTHF instead of THF	70
11[c]	EtOAc instead of THF	62
12[c,d]	$NaBiO_3$ (1.2 equiv)	52
13[c,d]	NFSI (1.2 equiv)	84
14[c,d]	dpmH (0.5 equiv)	80
15[c,d]	dpmH (0.5 equiv), NFSI (1.2 equiv)	92
16	without Co(dpm)$_2$	0
17[c,d]	without NFSI, $NaBiO_3$ (3.5 equiv)	9
18	without NFSI, without $NaBiO_3$	0

[a] Reaction conditions: **1a** (0.1 mmol), Co(dpm)$_2$ (0.02 mmol, 20 mol %), PivOH (0.05 mmol, 50 mol %), NFSI (0.15 mmol, 1.5 equiv), $NaBiO_3$ (0.2 mmol, 2 equiv), THF (1 mL), 80 °C. Co(dpm)$_2$ = bis(2,2,6,6-tetramethyl-3,5-heptanedionato)-cobalt(II) (CAS no. 13986-53-3). [b] ^{1}H NMR yields using dichloromethane as an internal standard. [c] $CoCl_2$ (20 mol %) and dpmH (0.1 mmol, 1 equiv) instead of Co(dpm)$_2$. [d] Solvent 2-MeTHF.

Intramolecular Amidation Substrate Scope. With the optimized reaction conditions in hand, we next examined the reaction scope with respect to amidoacrylate **1** (Table 2). We were pleased to find that a wide substrate **1** scope with *ortho*-, *meta*-, and *para*-substitution patterns gave intramolecular amidation products **2** in moderate to excellent yields. Using unsubstituted amido-3-phenylacrylate **1a**, product **2a** was obtained in 91% yield (Table 2, entry 1), which is consistent with optimization studies. Reaction upscaling to the gram scale did not affect the product yield (entry 2). Diverse functionalities at the phenyl group were well tolerated under the reaction conditions, such as alkyl (products **2b**, **2e**, **2g**, and **2l**), aryl (product **2k**), halides (**2d**, **2f**, and **2n**−**q**), methoxy

Table 2. Substrate Scope[a]



Entry	Structure	Product	Time	Yield, %
1		**2a** R = H	1.5 h	91
2[b]		**2a** R = H	2 h	92
3		**2b** R = Me	1 h	99
4		**2c** R = OMe	45 min	79
5		**2d** R = Br	1 h	84
6		**2e** R = R^1 = Me	1.5 h	84
7		**2f** R = F, R^1 = Cl	9 h	50
8		**2g**, R = Me	1.5 h	95
9		**2h**, R = OMe	45 min	76
10		**2i**, R = NHBoc	1 h	71
11		**2j**, R = $O(3\text{-}CF_3)C_6H_4$	2 h	70
12		**2k**, R = Ph	1.5 h	74
13		**2l**, R = Me	1.5 h	84
14[c]		**2m**, R = OMe	1.5 h	65
15		**2n**, R = F	6 h	70
16		**2o**, R = Cl	16 h	56
17		**2p**, R = Br	2 h	76
18		**2q**, R = I	4 h	59
19		**2r**	4 h	76
20		**2s**	16 h	89

[a] Reaction conditions: **1** (0.5 mmol), $CoCl_2$ (0.1 mmol, 20 mol %), dpmH (0.25 mmol, 50 mol %), PivOH (0.25 mmol, 50 mol %), NFSI (0.6 mmol, 1.2 equiv), $NaBiO_3$ (1.0 mmol, 2 equiv), 2-MeTHF (5 mL), 80 °C, isolated yields. [b] Reaction was performed starting from 1 g of substrate **1a**. [c] $CoCl_2$ (0.15 mmol, 30 mol %).

(**2c**, **2h**, and **2m**), trifluoromethyl phenyl ether (**2j**), and Boc-protected amino group (**2i**).

Both naphthyl amidoacrylates **1r** and **1s** formed indole products **2r** and **2s** in very good yields (entries 19 and 20). It is noteworthy that excellent regioselectivity was obtained using *meta*-substituted amido-3-phenylacrylates **1g**−**j**, and only intramolecular amidation products arising from the reaction of the less hindered C−H bond were observed (entries 8−11). Substrate scope screening revealed some limitations (Figure 3).

Unfortunately, amido-3-phenylacrylates containing an electron-withdrawing group (EWG), such as nitro (substrate **1t**) and cyano (**1u**), failed to give indole derivatives **2t,u** under standard reaction conditions, as well as substrate **1v** containing a nitro group at the double bond. Besides, it was found that carboxylic ester functionality is essential for intramolecular amidation (substrates **1w** and **1x**).

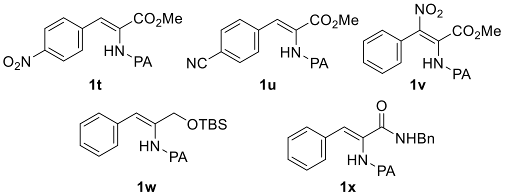
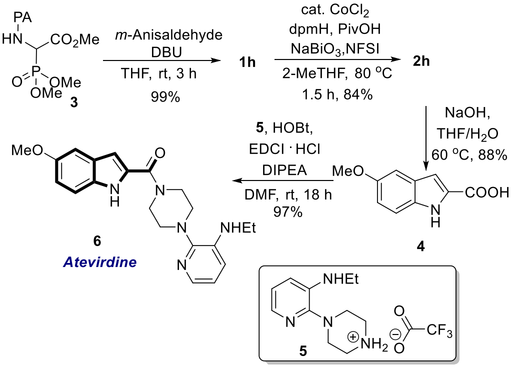


Figure 3. Intramolecular amidation substrate scope limitations.

The developed methodology application was demonstrated by the synthesis of an anti-HIV drug, atevirdine (Scheme 1).

Scheme 1. Synthesis of Atevirdine 6

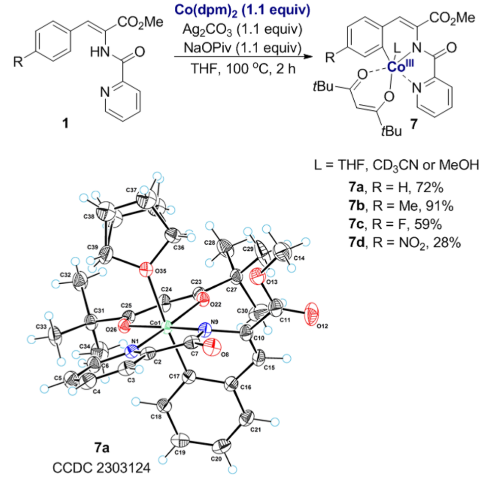


Atevirdine **6** was synthesized starting from *m*-anisaldehyde in four steps. Horner−Wadsworth−Emmons olefination was performed to yield amidoacrylate **1h** in quantitative yield, which was then subjected to our standard intramolecular amidation conditions to deliver indole carboxylate **2h** in 84% yield. The subsequent simultaneous picolinamide directing group removal and methyl ester hydrolysis under basic conditions furnished indole carboxylic acid **4** in 88% yield. Amide bond formation with piperazinium trifluoroacetate **5**, which was obtained in five steps from commercially available 2-chloro-3-nitropyridine, gave atevirdine with 97% yield.[10]

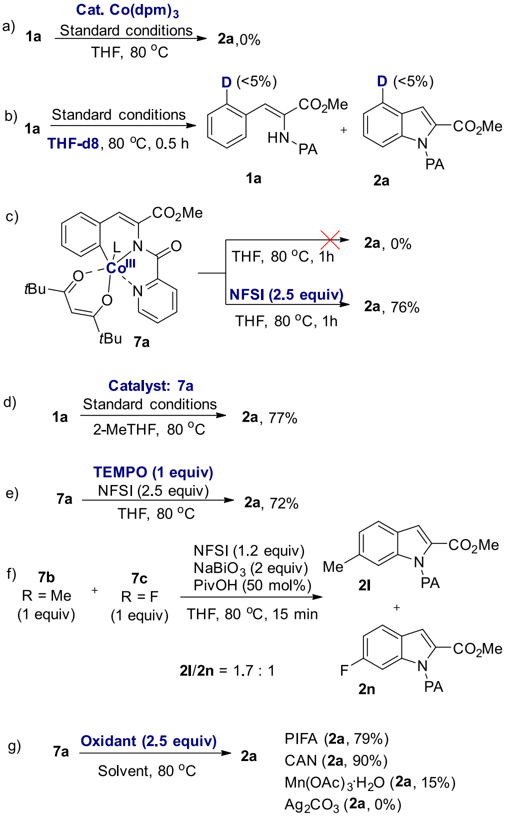
Mechanistic Studies. In our previous studies, we determined the intermediacy of C−H-activated Co(III) complex **7** in cobalt-catalyzed C−H activation and functionalization reactions of amidoacrylates and phenylalanine derivatives **1**.[4c,11] Therefore, in order to investigate the reaction mechanism, we synthesized different Co(III) complexes containing various substituents in the phenyl group. Cobalt(III) complexes **7a**−**d** were synthesized in low to good yields under oxidative conditions in the presence of NaOPiv base from the corresponding amidoacrylate **1** and a stoichiometric amount of $Co(dpm)_2$ (Scheme 2). The structure of complex **7a** was confirmed by X-ray crystallography (CCDC 2303124).[12]

In order to gain insight into the reaction mechanism, we conducted a series of control experiments (Scheme 3). First, we performed intramolecular amidation under standard reaction conditions by substituting $Co(dpm)_2$ catalyst with a $CoCl_3$/dpmH system and observed that substrate **1a** was unreactive (Scheme 3a). Such a result indicated that the first

Scheme 2. Synthesis of Cobaltacycles 7a−d and X-ray Crystal Structure of 7a



Scheme 3. Mechanistic Control Experiments



step of the catalytic cycle is the coordination of Co(dpm)$_2$ catalyst to the substrate **1a** and not the oxidation of Co(II) to Co(III), which is in accordance with literature data.[13] Next, we performed H/D scrambling experiments (Scheme 3b). By employing 0.1 mL of AcOH-d_4 instead of PivOH under standard reaction conditions at incomplete conversion, we observed <5% H/D scrambling in the *ortho*-position of substrate **1a** and <5% D incorporation in the *ortho*-position of the product **2a**, thereby indicating an irreversible C−H bond activation step. Next, to confirm the intermediacy of synthesized Co(III) complex **7a** we carried out stoichiometric, as well as catalytic, experiments (Scheme 3c,e,g). We observed that Co(III) complex **7a** forms intramolecular amidation product **2a** in 76% yield only in the presence of NFSI oxidant, which suggested the oxidatively induced reductive elimination pathway from high-valent Co(IV) species (Scheme 3c). Besides, indole **2a** was obtained in a similar yield using Co(III) complex **7a** as the reaction catalyst (Scheme 3d). To exclude the involvement of the radical reaction pathway, we performed an intramolecular amidation reaction using Co(III) complex **7a** under the standard reaction conditions by adding TEMPO as a radical scavenger (Scheme 3e). The presence of radical scavengers did not have a major impact on the outcome of the reaction, which indicated that the radical pathway most likely is not involved. Moreover, we performed competition experiments in the presence of NFSI and NaBiO$_3$ oxidants and PivOH additive using 4-methyl-substituted Co(III) complex **7b** and 4-fluoro-substituted Co(III) complex **7c** (Scheme 3f). We observed the formation of products **2l**/**2n** in a 1.7:1 ratio. Such a result is in accordance with experimental observations (Table 2) and might be explained by the lower energy barrier for the reductive elimination process of the corresponding Co(III) complex **7b**. Screening of commonly used oxidants for cobalt-catalyzed C−H bond functionalization revealed that phenyliodine(III) bis(trifluoroacetate) (PIFA) and ceric ammonium nitrate (CAN) are suitable oxidants for intramolecular C−N bond formation in compound **7a**, while Mn(OAc)$_3$, Ag$_2$CO$_3$, and NaBiO$_3$ did not yield the indole **2a** in acceptable yield (Scheme 3g). 4-Nitro-substituted Co(III) complex **7d** formed indole product **2t** when PIFA or CAN was used as the reaction oxidant but was unreactive in the presence of NFSI oxidant (Scheme 3h).[10] Presumably because of their different natures, the reaction pathways for NFSI, PIFA, and CAN may not be the same.

Cyclic Voltammetry Studies. Cyclic voltammetry (CV) is a great tool for the investigation of redox-involved reaction mechanisms.[14] CV data of **7a** are shown in Figure 4. Interestingly the CV data of Co(III) complex **7a** performed at room temperature and recorded from 0 to 1.8 V vs Ag/Ag+ at different scan rates showed three irreversible redox events (Figure 4a). The first redox event at the potential of $E^{p,ox}$ = 0.84 V vs Ag/Ag$^+$ (at 1600 mV/s scan rate) was assigned to the Co(III/IV) redox couple. The observed irreversibility indicated that **7a** was transformed into product **2a** upon oxidation, which suggests that intramolecular amidation of **1a** could be achieved in an electrosynthetic pathway.[7b] We confirmed indole **2a** formation under CV conditions by comparing CV data of Co(III) complex **7a** and indole **2a** (Figure 4b). Although a redox event at $E^{p,ox}$ = 1.52 V vs Ag/Ag$^+$ (at 1600 mV/s scan rate) was identified, we still had an unidentified one [approximately at $E^{p,ox}$ = 1.35 V vs Ag/Ag$^+$ (at 1600 mV/s scan rate)]. Computational studies revealed that the calculated Co(IV/V) redox standard potential is 1.67 V

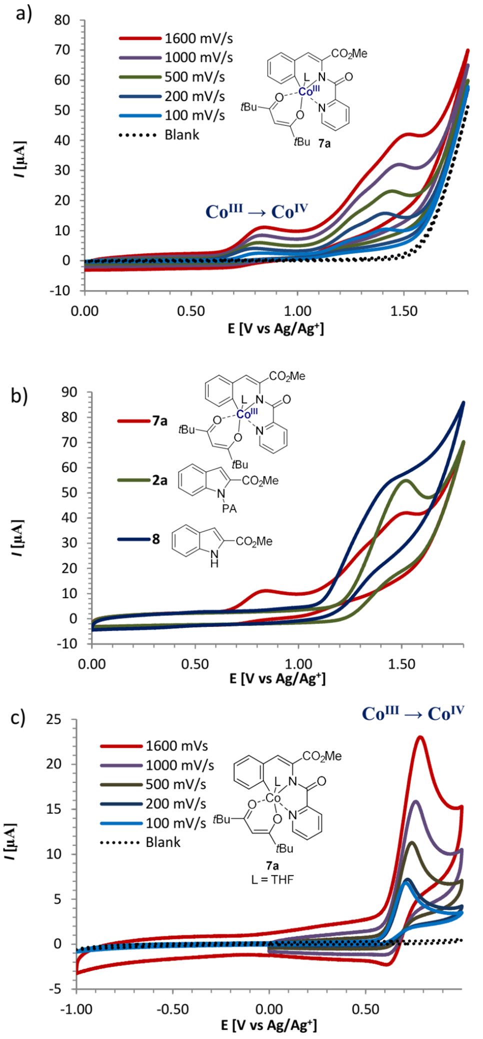


Figure 4. Cyclic voltammetry. Conditions: glassy carbon as working electrode, $Ag/AgNO_3$ (silver wire in 0.1 M NBu_4ClO_4/CH_3CN solution; $[AgNO_3]$ = 0.01 M; E^0 = −87 mV vs Fc/Fc^+ couple) reference electrode and a platinum wire counter electrode, $n Bu_4PF_6$ (0.2 M), **7a** (or **2a**, **8**) (0.002 M) in dry THF. (a) CV of **7a** at rt, recorded at different scan rates; (b) CV of **7a**, **2a**, and **8** at rt, recorded at a scan rate of 1600 mV/s; and (c) CV of **7a** at 0 °C, recorded at different scan rates.

(referenced to the Ag/Ag^+ electrode),[15] which is higher than the oxidation potentials of indole product **2a**. Therefore, it is unlikely that the Co(V) species are involved in cobalt-catalyzed intramolecular amidation. In order to determine the unidentified redox event, we synthesized indole **8** with a cleaved picolinamide directing group. Pleasingly, the CV of **8** ($E^{p,ox}$ = 1.38 V vs Ag/Ag^+ at 1600 mV/s scan rate) showed a match (Figure 4b). When the CV experiment of **7a** was performed at a lower temperature (0 °C) (Figure 4c) at a 1600 mV/s scan rate, we observed a quasireversible redox event for Co(III/IV), which is consistent with the observations made by the Ackermann group.[7a]

To explore the redox potential correlation with the amidoacrylate **1** substituent electronic properties, we conducted CV experiments for several Co(III) complexes **7a−d** containing electronically different substituents (Figure 5).

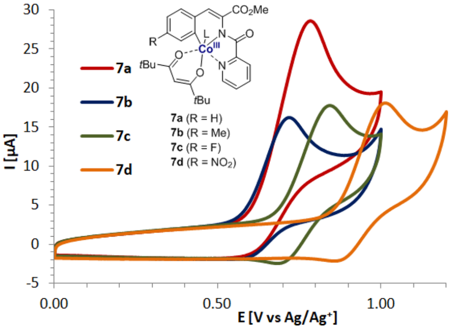


Figure 5. Cyclic voltammetry. Conditions: glassy carbon as working electrode, $Ag/AgNO_3$ (silver wire in 0.1 M NBu_4ClO_4/CH_3CN solution; $[AgNO_3]$ = 0.01 M; E^0 = −87 mV vs Fc/Fc^+ couple) reference electrode and a platinum wire counter electrode, $n Bu_4PF_6$ (0.2 M), **7a−d** (0.002 M) in dry THF, recorded from 0 to 1.2 V vs Ag/Ag^+ at a scan rate of 1600 mV/s.

Computational Studies. To better understand the intramolecular amidation reductive elimination step, density functional theory (DFT) calculations were carried out. A small benchmark of the DFT methods was performed to establish the most suitable calculation method for geometry optimization. To this end, a geometry of Co(III) complex **7a** was optimized using B3LYP-D3BJ, BVP86, wB97XD, m062x-D3, PBE1PBE-D3BJ, and TPSSTPSS-D3BJ methods. The optimized geometries were compared with the X-ray structure of complex **7a** by comparing the lengths of N1−Co, N2−Co, C1−Co, O1−Co, O2−Co, and O3−Co bonds.[10] The best overall geometry was obtained with the BVP86 method. Therefore, the BVP86 method was used for further structure optimization to determine the potential energy profile of reductive elimination. The DFT calculations showed that the transition state of the reductive elimination of Co(III) complex in a singlet state [TS-Co(III)s] is favored compared with that of Co(III) complex in a triplet state [TS-Co(III)t] (Figure 6).

Similarly, the transition state of the reductive elimination of the Co(IV) complex in duplet state [TS-Co(IV)d] is favored over that of the Co(IV) complex in quartet state [TS-Co(IV)q]. Therefore, the full potential energy surface of the reductive elimination was calculated for the Co(III) complex in singlet state [TS-Co(III)s] (Figure 6a) and Co(IV) complex in duplet state [TS-Co(IV)d] (Figure 6b). Reductive elimination starting from the Co(IV) complex [SM-Co(IV)d] is energetically favored (16.5 kcal/mol) compared with reductive elimination starting from the Co(III) complex SM-Co(III)s (26.7 kcal/mol). Furthermore, reductive elimination of Co(III) complex SM-Co(III)s to Co(I) complex PDT-Co(I)s is thermodynamically unfavorable (15.5 kcal/mol), while the Co(IV) complex SM-Co(IV)d to Co(II) complex PDT-Co(II)d is thermodynamically favorable (−7.0 kcal/

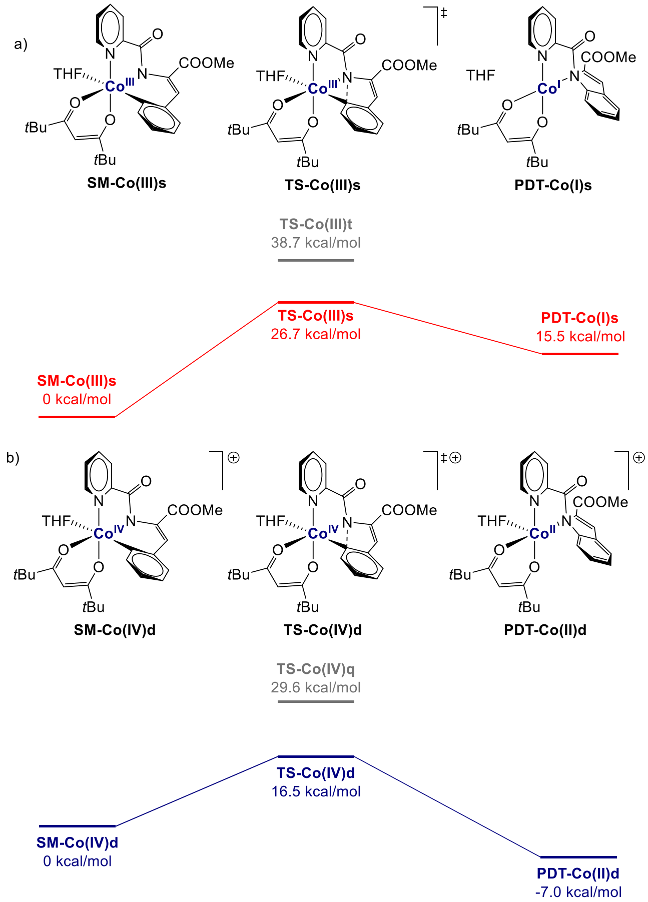


Figure 6. Potential energy surface comparison of reductive elimination step starting from (a) SM-Co(III) to PDT-Co(I) and (b) SM-Co(IV) to PDT-Co(II).

mol). Therefore, DFT calculations show that the reductive elimination proceeds via C−N bond formation in the transition state TS-Co(IV)d by changing the cobalt oxidation state from Co(IV) to Co(II). These computational studies are in agreement with our experimental observations.

Next, a small benchmark of DFT methods was performed to establish the most suitable calculation method for the redox standard potential (E^0) calculations for Co(III/IV) and Co(IV/V). The absolute standard potential values of Co(III/IV) redox reaction were obtained using the Nernst equation and then referenced to the Ag/Ag+ electrode.[10] The wB97XD/Def2SVP method using the SMD solvation model provided the closest standard potential (0.66 V) to the experimentally determined value ($E^{1/2}_{\mathrm{exp}}$ = 0.68 V). Therefore, the wB97XD method single-point energy calculations using the Def2TZVP basis set and both PCM and SMD solvation models were performed. Interestingly, calculations with an increased basis set did not provide a better correlation between calculated (0.66 V, SMD) and experimentally determined ($E^{1/2}_{\mathrm{exp}}$ = 0.68 V) potential. As a result, the standard potential of other Co(III) complexes was calculated by using the wB97XD/Def2SVP SMD (THF)//wB97XD/Def2SVP method. The method was further validated by performing calculations of Co(III/IV) standard potentials for methyl (**7b**), fluoro (**7c**), and nitro (**7d**) substituent-containing Co(III) complexes. The selected computational method provided slightly underestimated redox standard potentials for complexes **7c** (E^{0}_{calc} = 0.67 V and $E^{1/2}_{\mathrm{exp}}$ = 0.74 V), **7b** (E^{0}_{calc} = 0.59 V and $E^{1/2}_{\mathrm{exp}}$ = 0.64 V) and **7d** (E^{0}_{calc} = 0.91 V and $E^{1/2}_{\mathrm{exp}}$ = 0.91 V) (Figure 7).

Nevertheless, a good overall correlation between the calculated and experimental redox potentials of Co(III/IV) was observed.

Proposed Reaction Mechanism. On the basis of the control experiments, CV, and computational studies, we propose the reaction mechanism (Scheme 4), which involves the Co(II)/Co(IV) catalytic cycle. Initially, the Co(dpm)$_2$ catalyst, which is prepared in situ from CoCl$_2$ and dipivaloylmethane ligand, coordinates with amidoacrylate substrate **1a** to form Co(II) complex **A**. Next, oxidation of Co(II) complex **A** takes place to form Co(III) complex **B**, which undergoes C(sp^2)−H bond cobaltation to form Co(III) complex **C**. Oxidation of Co(III) intermediate **C** to high-valent Co(IV)

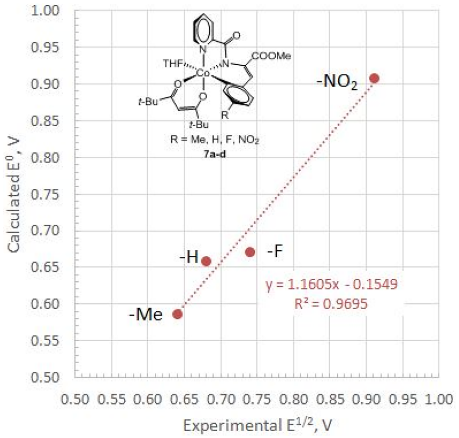
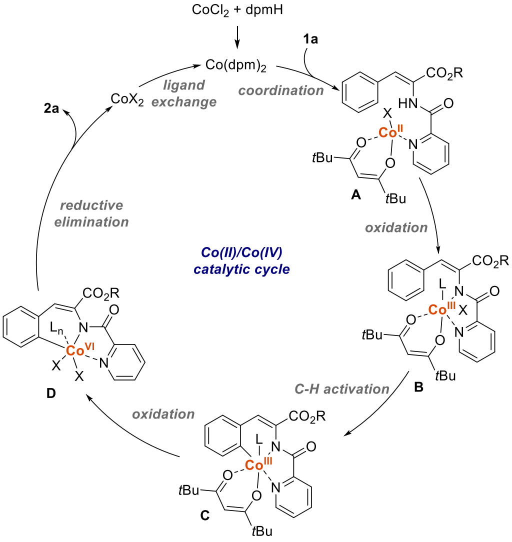


Figure 7. Correlation between calculated redox standard potentials and experimental $E^{1/2}$ value for Co(III) complexes **7a**−**d**.

Scheme 4. Proposed Reaction Mechanism



species gives complex **D**, which undergoes fast reductive elimination to liberate product **2a** and cobalt(II) species, which after ligand exchange restarts the catalytic cycle.

■ CONCLUSION

Nowadays, the Co(II)/Co(III)/Co(I) catalytic cycle for the high-valent cobalt-catalyzed C−H bond functionalization methodology is relatively well studied. Nevertheless, there are several discovered methodologies that are not consistent with the Co(II)/Co(III)/Co(I) mechanism, and such methods continue to be discovered. So far, the pathway, which involves oxidatively induced reductive elimination (containing detailed indisputable evidence of the involvement of Co(IV) species), is presented only in two literature reports. The lack of reports on the oxidatively induced reductive elimination (ORE) pathway for cobalt catalysis might be associated with the difficulties to obtain evidence, which arises from the high reactivity of Co(IV) species.

In summary, we have developed an efficient protocol for the synthesis of indole-2-carboxylic esters via intramolecular amidation of amidoacrylates. We synthesized several Co(III) complexes, confirmed their intermediacy in intramolecular amidation reactions, and studied their chemical reactivity, as well as electrochemical behavior. Performed mechanistic experiments, cyclic voltammetry, and computational studies supported an oxidatively induced reductive elimination pathway, which involves high-valent Co(IV) species for intramolecular amidation reaction of amidoacrylates **1**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c05706.

> Experimental procedures and characterization data for all new compounds, along with copies of the NMR spectra, crystallographic data, cyclic voltammetry studies, and computational studies (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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DEDICATION

Dedicated to Prof. Dr. Aigars Jirgensons on his 50th Birthday.

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Synthesis of 3-Benzazepines via Cobalt-Catalyzed C−H Bond Functionalization with CaC_2 as the Acetylene Source

Aleksandrs Cizikovs,‡ Paula A. Zagorska,‡ and Liene Grigorjeva*

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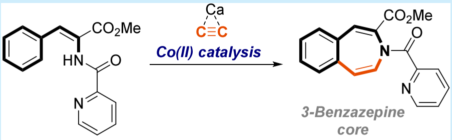
ABSTRACT: Herein, we report a simple method for the synthesis of 3-benzazepine derivatives via a cobalt-catalyzed, picolinamide-directed α-amidoacrylate C(sp^2)−H bond functionalization approach. The reactions utilize calcium carbide as an inexpensive, easy-to-handle, and solid acetylene source, and simple $CoCl_2$ as the reaction catalyst. Excellent functional group tolerance is observed, yielding diverse substituted 3-benzazepine derivatives in good to excellent yields.



- 20 examples, yield up to 99%
- CaC_2 as inexpensive and easy-to-handle alkyne source
- Gram scalability
- Broad substrate scope

3-Benzazepines and particularly their hydrogenated derivatives are important structural motifs due to their prevalence in a wide variety of relevant compounds, including isolated natural products, biologically active alkaloids, agrochemicals and pharmaceuticals.[1] For example, the alkaloids turkiyenine,[2a] cephalotaxine[2b] and bulgaramine,[2c] which are bioactive components isolated from a number of plants used in medicine, as well as antiobesity drug lorcaserin[2d] and bradycardic agent zatebradine[2e] (Figure 1).

In addition, 3-benzazepine derivatives containing different substitution patterns are widespread multifunctional key intermediates for the synthesis of pharmaceutically active compounds. Therefore, the development of new methods for the synthesis of the benzazepine core is highly desirable.

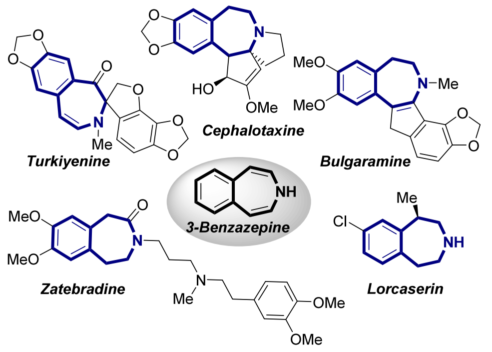


Figure 1. Representative examples of pharmaceutically relevant 3-benzazepine derivatives.

In the past two decades C−H bond functionalization using cobalt(II) salts in combination with bidentate directing groups[3] has been widely explored and has become an efficient tool for the construction of various valuable heterocycles.[4] Recently, we have demonstrated that α-amidoacrylates **1**, which were obtained from commercially available benzaldehydes in one step, are versatile substrates for cobalt-catalyzed C−H bond functionalization reactions, giving easy and convenient access to a variety of heterocyclic compounds (Scheme 1). For example, 1-oxo-1,2-dihydroisoquinoline derivatives were obtained via C−H bond carbonylation (Scheme 1, a).[5a] The C−H bond imination of α-amidoacrylate efficiently provided 1-aminoisoquinoline derivatives (Scheme 1, b).[5b] The indole-2-carboxylate derivatives were obtained via intramolecular amidation of α-amidoacrylates under oxidative reaction conditions (Scheme 1, c).[5c]

In the few past decades the use of calcium carbide as an inexpensive and solid acetylene gas source has significantly increased.[6] Although there are numerous reports on the use of calcium carbide in transition metal-catalyzed transformations,[7] to our knowledge there are no reports on the use of CaC_2 for directed C−H bond functionalization as an alkyne source.

Herein we report an efficient and concise method for the construction of 3-benzazepine core via cobalt-catalyzed, picolinamide-directed C(sp^2)−H bond annulation reaction of

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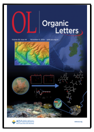

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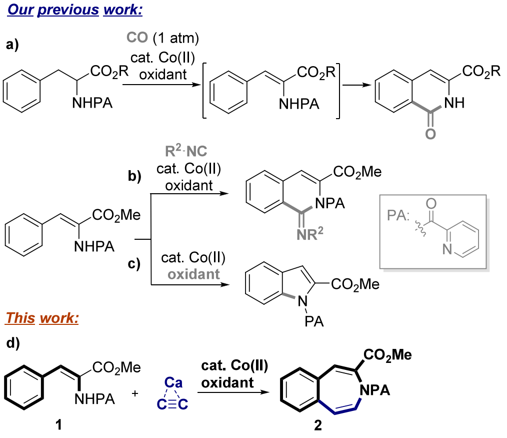
Scheme 1. Cobalt-Catalyzed C−H Bond Functionalization of α-Amidoacrylates 1

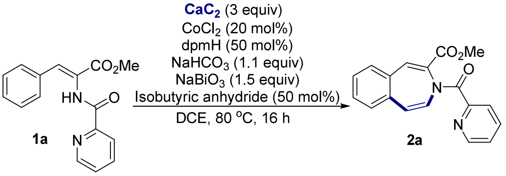


α-amidoacrylate substrates **1**, using calcium carbide as an acetylene gas source (Scheme 1, d).

For the optimization studies (Table 1)[8] we used α-amidoacrylate **1a** as a model substrate and commercially available CaC_2 as an acetylene source, which was additionally grounded to powder consistency.

We were pleased to find that, by employing a similar catalytic system that had shown good reactivity in our previous studies,[5c] we could observe the formation of corresponding 3-benzazepine derivative **2a** in 24% yield (Table 1, entry 1). Substituting NaOPiv base with Na_2CO_3 increased the product **2a** yield to 66% (entry 2), and further screening revealed that $NaHCO_3$ was the optimal base additive providing product **2a** in 93−99% yield (entries 3−4). Other oxidants, for example, Ag_2CO_3 and $NaBO_3$, were less effective (entries 5−6). In addition, other solvents such as toluene (entry 7) and 2-MeTHF (entry 8) gave 83% and 48% yields of **2a**, respectively. We found that the addition of isobutyric anhydride plays a crucial role for the successful transformation, as the reaction excluding the anhydride gave only 30% yield of **2a** (entry 9). The replacement of isobutyric anhydride with acetic anhydride (entry 10) or pivaloyl anhydride (entry 11) resulted in decreased product **2a** yield. Several C−H functionalization reactions are known in which the addition of an anhydride significantly improved the product yield. This might be explained by the fact that the anhydride acts as a ligand for the metal catalyst, thus accelerating the transformation.[9] Besides, it is worth mentioning that in the control experiment without a cobalt catalyst or dipivaloylmethane ligand, or an oxidant, the formation of 3-benzazepine **2a** was not observed (entries 12−14).

Table 1. Optimization of Reaction Conditions[a]



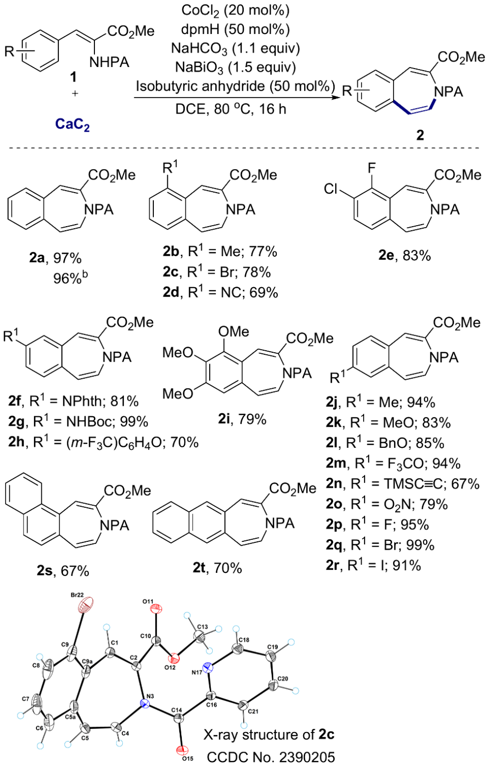
entry	change from above conditions	yield, %[b]
1	NaOPiv (2 equiv) instead of $NaHCO_3$	24
2	Na_2CO_3 (2 equiv) instead of $NaHCO_3$	66
3	$NaHCO_3$ (2 equiv)	93
4	**none**	**99**
5	Ag_2CO_3 instead of $NaBiO_3$	40
6	$NaBO_3$ instead of $NaBiO_3$	46
7	Toluene instead of DCE	83
8	2-MeTHF instead of DCE	48
9	w/o isobutyric anhydride	30
10	$(Ac)_2O$ instead of isobutyric anhydride	68
11	$(Piv)_2O$ instead of isobutyric anhydride	65
12	w/o $CoCl_2$	0
13	w/o dipivaloylmethane (dpmH)	0
14	w/o $NaBiO_3$	0

[a] Reaction conditions: **1a** (0.1 mmol), CaC_2 (0.3 mmol, 3 equiv), $CoCl_2$ (0.02 mmol, 20 mol %), dpmH (0.05 mmol, 50 mol %), $NaHCO_3$ (0.11 mmol, 1.1 equiv), $NaBiO_3$ (0.15 mmol, 1.5 equiv), isobutyric anhydride (0.05 mmol, 50 mol %), DCE (1 mL), 80 °C. [b] NMR yield using iodoform as an internal standard. dpmH = dipivaloylmethane.

Next, the scope of substituted amidoacrylates **1** containing diverse functional groups was examined under the optimized conditions (Scheme 2). Under the standard reaction conditions, we were able to isolate benzazepine **2a** in 97% yield. Scaling up the reaction to gram-scale gave product **2a** in 96% yield, thus demonstrating that the developed method can be scaled up without a loss of efficiency. We were pleased to find that a wide substrate **1** scope with *ortho-*, *meta-* and *para*-substitution patterns gave products **2** in good to excellent yields. Using *meta*-substituted substrates **1f−h**, we observed excellent regioselectivity and obtained 3-benzazepines **2f−h** arising from functionalization of the less hindered C−H bond, which is consistent with our previous observations.[5] Various functional groups were tolerated under the reaction conditions, including electron donating groups such as methyl (products **2b**, **2j**) and methoxy (**2i**, **2k**) and rather strong electron withdrawing groups such as cyano (**2d**) and nitro groups (**2o**). In addition, in the case of halogenated substrates **1**, it was possible to obtain products **2c**, **2e**, and **2p−r** with very good to excellent yields (78−99%). The structure of product **2c** was unambiguously established by a single-crystal X-ray study (Scheme 2). Sterically hindered amidoacrylates **1e** and **1i** gave the corresponding 3-benzazepines **2e** and **2i** in very good yields, 83% and 79%, respectively. Interestingly, substrates containing protected amino groups (**1f** and **1g**) were competent substrates and provided the corresponding 3-benzazepines **2f** and **2g** in excellent yields. Additionally, we demonstrated that both 1- and 2-naphthalenyl amidoacrylates **1s** and **1t** were reactive under the reaction conditions giving access to naphthoazepines **2s** and **2t**.

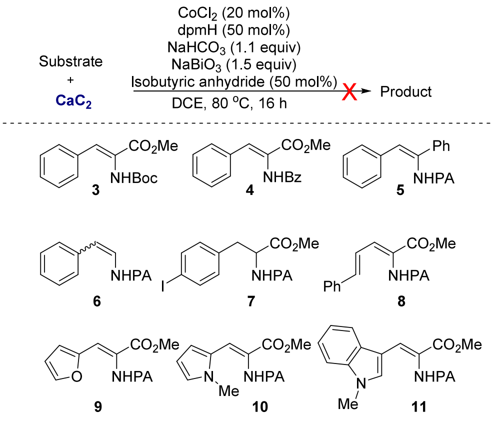
While studying the scope of the developed method, we found some limitations (Scheme 3). We found that employment of a picolinamide directing group was essential, as amidoacrylates **3** and **4** were unreactive. Product formation was not observed in the case of substrates **5** and **6**, suggesting that the ester functionality is necessary for successful transformation. Phenylalanine derivatives **7**, as well as substrate **8**, under standard reaction conditions, formed only trace amounts of corresponding products. Unfortunately α-amidoacrylates containing heterocyclic rings, such as furane (substrate **9**), *N*-methyl pyrrole (substrate **10**) and *N*-methylindole

Scheme 2. Substrate Scope[a]



[a] Reaction conditions: **1** (0.5 mmol), CaC_2 (1.5 mmol, 3 equiv), $CoCl_2$ (0.1 mmol, 20 mol %), dpmH (0.25 mmol, 50 mol %), $NaHCO_3$ (0.55 mmol, 1.1 equiv), $NaBiO_3$ (0.75 mmol, 1.5 equiv), isobutyric anhydride (0.25 mmol, 50 mol %), DCE (5 mL), 80 °C, 16 h, isolated yields. [b] Standard conditions, starting from 1g (3.55 mmol) **1a**.

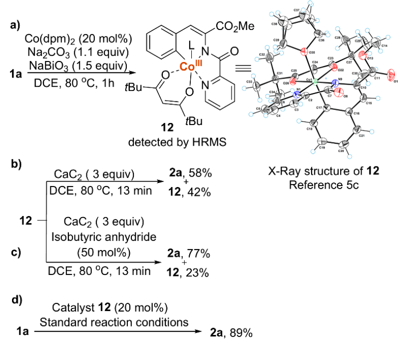
Scheme 3. Unsuccessful Substrates



(substrate **11**) under standard reaction conditions gave only product traces, which was determined by ^{1}H NMR spectra, suggesting that different reaction conditions in the case of heterocyclic substrates should be applied (Scheme 3).

In order to gain insight into the reaction mechanism, several mechanistic control experiments were conducted (Scheme 4).

Scheme 4. Mechanistic Control Experiments

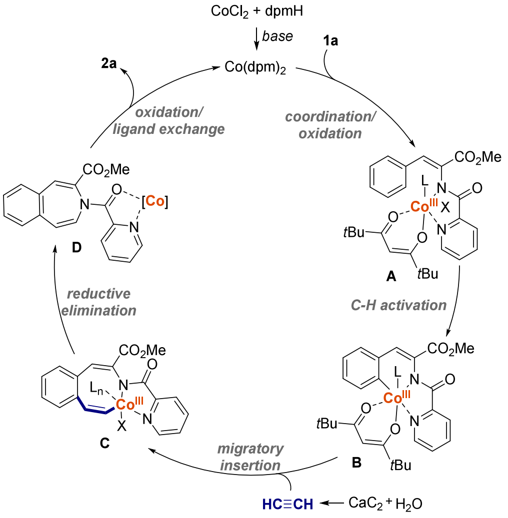


First, we managed to detect Co(III) complex **12** in the reaction mixture by HRMS analysis (Scheme 4, a)). We synthesized Co(III) complex **12** according to our previously described method[5c] and confirmed its intermediacy in our reaction (Scheme 4, b−d). Stoichiometric experiments using Co(III) complex **12** as substrate were analyzed at incomplete conversion in the absence (Scheme 4, b) and in the presence of isobutyric anhydride (Scheme 4, c) to determine the role of isobutyric anhydride as potential ligand for cobalt intermediates. Obtained results indicate that in the presence of isobutyric anhydride, the reaction is slightly accelerated, suggesting the ligand role for isobutyric anhydride. Reaction under standard reaction conditions using Co(III) complex **12** as the reaction catalyst yielded 89% of benzazepine **2a**, which was determined by ^{1}H NMR data (Scheme 4, d).

Based on the control experiments and our previous mechanistic studies,[5] we propose the plausible catalytic cycle (Scheme 5). Initially, the $Co(dpm)_2$ catalyst, which forms *in situ* from $CoCl_2$ and dipivaloylmethane in the presence of a base, coordinates with amidoacrylate **1a** and is oxidized to Co(III) complex **A**. Next, the C(sp^2)−H bond cobaltation takes place to form the Co(III) complex **B**. It is possible that complex **B** undergoes ligand exchange to replace dipivaloylmethane with isobutyrate ligand prior to the migratory insertion step. Next, coordination and insertion of acetylene form complex **C**, followed by reductive elimination to yield **D**. After demetalation, cobalt(III) intermediate **D** liberates **2a** and cobalt is reoxidized to restart the catalytic cycle. It is worth mentioning that acetylene is produced *in situ* by slow-release mode from CaC_2 and proton source arising from reagents, solvent and moisture.[10]

In summary, we have developed a novel approach for the synthesis of 3-benzazepine derivatives through cobalt-catalyzed, picolinamide-directed C(sp^2)−H bond annulation with acetylene. This method employs calcium carbide as an efficient, solid, and easy-to-handle acetylene source. Notably, the reaction exhibits a very good functional group tolerance,

Scheme 5. Plausible Mechanism



and it allows obtaining the challenging unsaturated benzazepine core in very good yields.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c03551.

Detailed experimental procedures, complete optimization table, characterization data of starting materials and products, copies of ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra of these compounds, and crystallographic data (PDF)

Accession Codes

Deposition Number 2390205 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Author Contributions

‡A. Cizikovs and P. A. Zagorska contributed equally.

Notes

The authors declare no competing financial interest.

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(10) For details, see the Supporting Information (section 2.4.1.).

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Cobalt-Catalyzed C–H Bond Functionalization: a Personal Account

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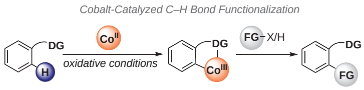

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Abstract The development of green and sustainable synthetic methods is of great interest worldwide. Today the direct activation and functionalization of relatively inert C–H bonds is one of the top fields in organic chemistry, and this strategy already represents a sustainable and more environmentally friendly approach due to its atom and step economy compared to alternative C–C and C–Het bond-forming processes. Much progress has been made in developing C–H bond functionalization methods using noble-metal catalysts. Cobalt has recently emerged as an attractive alternative because it is less toxic, cheaper, and more abundant than noble metals. This Account summarizes the cobalt-catalyzed C–H bond-functionalization methods that have been developed during the corresponding author's research career.
1 Introduction and Background
2 C–H Bond Functionalization of 8-Aminoquinoline Benzamides
3 Mechanistic Investigations of Cobalt-Catalyzed, Aminoquinoline-Directed C–H Bond Functionalization of Benzamides
4 C(sp^2)–H Bond Functionalization of 8-Aminoquinoline Phosphinamides
5 C(sp^2)–H Bond Carbonylation of 8-Aminoquinoline Sulfonamides
6 C(sp^2)–H Bond Functionalization of Benzoic Acids
7 C(sp^2)–H Bond Functionalization of Phenylglycine Derivatives
8 C(sp^2)–H Bond Functionalization of Phenylalanine Derivatives
9 Conclusion

Key words amino acid, annulations, carbonylation, C–H bond activation, cobalt catalysis, imination, intramolecular amidation

1 Introduction and Background

Nowadays direct functionalization of the ubiquitous, but at the same time relatively inert C–H bonds is one of the most active research fields in organic chemistry. Transition-metal-catalyzed C–H bond activation and functionalization with a broad selection of coupling partners is an atom- and step-economical methodology that allows avoiding lengthy synthetic schemes and reduce undesired byproducts.[1] In recent decades it has become an essential and irreplaceable tool for the construction of a wide variety of useful molecules.[2] Impressive progress has been made in the development of highly efficient transformations through noble-transition-metal-catalyzed C–H bond functionalization, despite their expensiveness, low natural abundance, and potential toxicity. The C–H bond functionalization using first-row transition-metal catalysts (Mn, Fe, Co, Ni, Cu) has emerged as an attractive alternative to noble metals due to their low cost and environment-friendly properties.[3] Due to the unique reactivity, lower toxicity and earth abundance cobalt is considered a sustainable metal. Therefore, in the last decade, the development of new methods for C–H bond functionalization using cobalt catalysis has been of particular interest.[4] Cobalt-catalyzed C–H bond functionalization methods fall into two main categories depending on the reaction conditions and the cobalt catalyst used to activate the C–H bond. The first category is low-valent cobalt catalysis, where C–H bond activation is performed by Co(0), Co(I), or Co(II) species mainly under reductive conditions.[4a] A breakthrough in low-valent cobalt catalysis occurred in 2010 when Yoshikai's group developed an efficient C(sp^2)–H bond-functionalization methodology.[5] Since then, this approach has been widely applied for the development of new transformations.[4d] The second category is high-valent cobalt catalysis, where the active species that perform C–H bond-activation step is Co(III), typically under oxidative or nonreductive reaction conditions.[4a] In 2013, Kanai, Matsunaga, and co-workers reported the first studies on Cp*Co(III)-catalyzed functionalization of the C–H bonds,[6] leading to a breakthrough in the C–H activation field.

Under this background, our research group was focused on the cobalt-catalyzed C–H bond activation and functionalization. In this Account, we summarize the developed cobalt-catalyzed C–H bond-functionalization methods and mechanistic investigations.

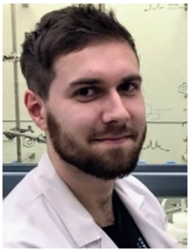
2 C–H Bond Functionalization of 8-Aminoquinoline Benzamides

At the end of 2013, Liene Grigorjeva joined Prof. Olafs Daugulis group at the University of Houston as a postdoctoral researcher. Inspired by the excellent reports on C–H bond activation under Cp*Co(III) catalysis we aimed to explore and contribute to this research area.

In 2014, we discovered a novel concept, which demonstrated that simple Co(II) salts in combination with bidentate directing group assistance efficiently can be exploited as high-valent Co(III) precursors for the C–H bond-activation process. We developed a very simple catalytic system for the successful benzamide **1** C(sp^2)–H bond activation,

Biographical Sketches

Aleksandrs Cizikovs was born in Riga (Latvia). He received his MSc degree in 2022 from the University of Latvia and is currently working on his PhD degree under the supervision of Dr. L. Grigorjeva at the Latvian Institute of Organic Synthesis. His research interests are focused on transition-metal-catalyzed C–H bond functionalization.

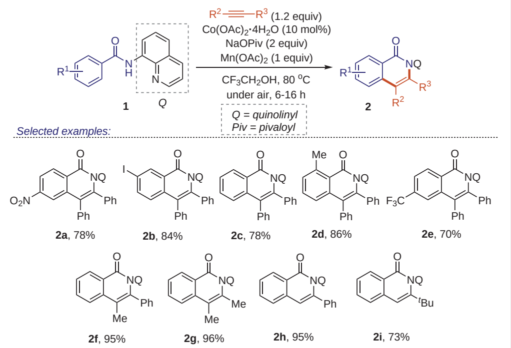


Lukass Lukasevics was born in Riga (Latvia). He obtained his PhD degree from Riga's Technical University in 2022 under the guidance of Dr. Grigorjeva. Since 2022 he has been a postdoctoral researcher with Prof. O. Daugulis at the University of Houston. His research interests involve transition-metal catalysis and organometallic chemistry.

Paula Amanda Zagorska was born in Riga (Latvia). She is currently a 4th year undergraduate student under the supervision of Dr. L. Grigorjeva. Her research interests include organic and organometallic chemistry.

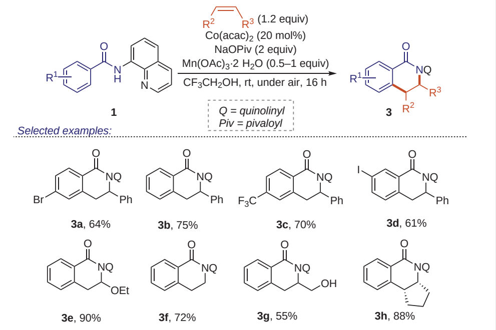
Liene Grigorjeva was born in Tukums (Latvia). She studied chemistry at Riga Technical University where she obtained bachelor's (2007) and master's (2009) degrees. From 2009 to 2013 she was working as a PhD student at the Latvian Institute of Organic Synthesis under the supervision of Prof. A. Jirgensons. After postdoctoral studies with Prof. O. Daugulis at the University of Houston (2013–2016) she became a principal researcher at the Latvian Institute of Organic Synthesis and assistant professor at Riga Technical University. Her main research interests are cobalt-catalyzed C–H bond functionalization, C–H oxidation reactions, and the development of organic synthesis methodology.

followed by functionalization with terminal and internal alkynes. The reaction employed inexpensive and commercially available Co(II) acetate as the catalyst, NaOPiv as the base, Mn(II) acetate, and oxygen from the air as the reaction oxidants. We demonstrated that the developed method is highly general, tolerating a large number of various functional groups (Scheme 1).[7] We managed to characterize the C–H activated Co(III) complex using ^{1}H and ^{13}C NMR data. Besides, the C–H activated Co(III) complex was isolated from the stoichiometric benzamide **1** reaction with Co(II) acetate under oxidative reaction conditions, thus demonstrating the formation of tridentate Co(III) pincer type complex.



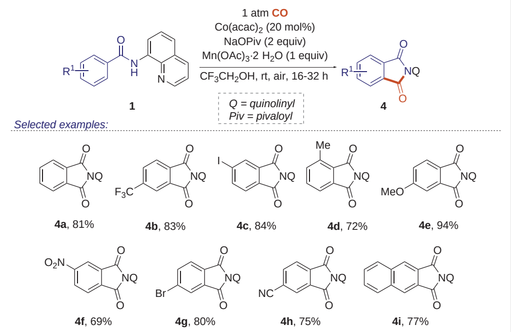
Scheme 1 Cobalt-catalyzed, 8-aminoquinoline-directed benzamide **1** C–H bond annulation with alkynes

We further demonstrated this concept for the aminoquinoline benzamide **1** C(sp^2)–H functionalization with alkenes (Scheme 2).[8] In this case, the reaction employed Co(acac)$_2$ as the catalyst, NaOPiv as the base, and Mn(III) acetate as the oxidant. The reaction proceeded smoothly even at room temperature yielding products **3** in good yields.



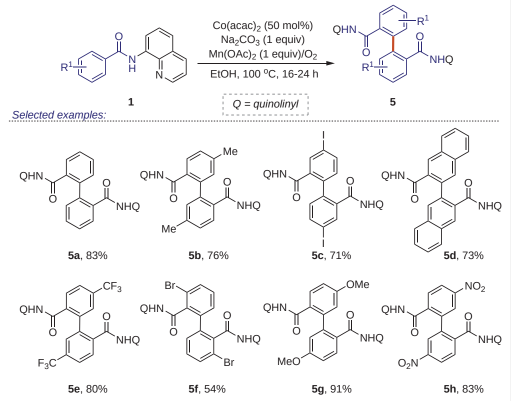
Scheme 2 Cobalt-catalyzed, 8-aminoquinoline-directed benzamide **1** C–H bond annulation with alkenes

Pleasingly, the reaction conditions we used for the functionalization of the aminoquinoline benzamide C(sp^2)–H bond with alkenes were successful also for C(sp^2)–H bond carbonylation using CO gas at atmospheric pressure (Scheme 3).[9]



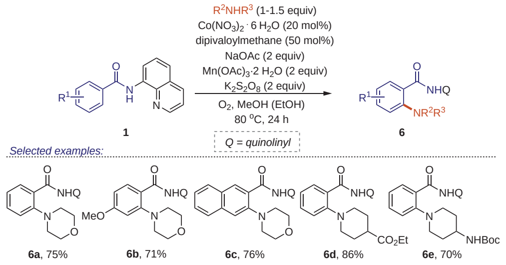
Scheme 3 Cobalt-catalyzed, 8-aminoquinoline-directed benzamide **1** C–H bond carbonylation with CO

In 2015, we demonstrated that even aminoquinoline-directed, cobalt-promoted homocoupling (dimerization) of benzamides **1** could be achieved. Similarly to previous methods, we used Co(acac)$_2$ as the catalyst, reactions were carried out in ethanol solvent in the presence of Mn(OAc)$_2$, oxygen as the oxidant, and Na$_2$CO$_3$ as the base (Scheme 4).[10] We demonstrated, that the reactions are tolerant to various functional groups, including the halogen atoms, nitro, ether, and ester functionalities. Additionally, we demonstrated that the cross-coupling of aminoquinoline benzamides occurs in moderate yields and selectivity when electronically different amides are used.



Scheme 4 Cobalt-promoted, 8-aminoquinoline-directed dimerization of benzamides **1**

In the same year we discovered the aminoquinoline benzamide **1** C(sp^2)–H bond-amination reaction. The reaction employed *in situ* prepared Co(II) dipivaloylmethane as the catalyst, which was prepared from the Co(II) nitrate and dipivaloylmethane under basic conditions. The optimized reaction conditions employed NaOAc as the base, Mn(III) acetate and $K_2S_2O_8$ as the oxidants and was heated in the presence of O_2 in alcohol solvent (Scheme 5). However, the amination reaction of benzamides **1** was not investigated further, as the reaction under cobalt catalysis appeared to be limited to six-membered-ring amines.[11]



Scheme 5 Cobalt-catalyzed, 8-aminoquinoline-directed benzamide **1** C–H bond amination

3 Mechanistic Investigations of Cobalt-Catalyzed, Aminoquinoline-Directed C–H Bond Functionalization of Benzamides

During the last decade significant mechanistic investigations, including isolation of potential organometallic cobalt intermediates, kinetic studies, DFT calculations, and others were performed on cobalt-catalyzed, bidentate chelation-assisted C(sp^2)–H bond activation and functionalization allowing us to understand the general reaction mechanism and elementary steps.[12] Besides, over the years it has also become clear that different C–H functionalization coupling partners may lead to distinct catalytic cycles involving Co(III) or Co(IV) species as the key intermediates.

Although some preliminary mechanistic studies were conducted almost a decade ago during methodology development, a detailed mechanistic investigation of cobalt-catalyzed, aminoquinoline-directed benzamide C(sp^2)–H functionalization was published only recently in 2025, in collaboration with the group of Prof. O. Daugulis.[11b]

In this detailed mechanistic study, we synthesized and characterized several types (compounds **7**–**11**) of the potential organometallic cobalt(III) intermediates (Figure 1).[11b] We managed to isolate and characterize by XRD analysis the Co(III) complex **10** arising from migratory insertion into carbon–carbon bonds.

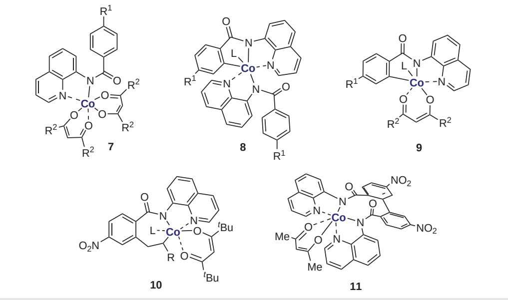
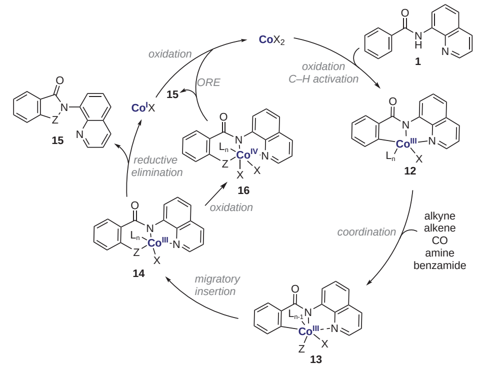


Figure 1 Synthesized and characterized potential Co(III) intermediates

The reactivity of all intermediates in stoichiometric and catalytic reactions was explored. Obtained results along with the kinetic and cyclic voltammetry studies allowed us to determine that two types of catalytic cycles are operative for our developed cobalt-catalyzed, aminoquinoline-directed benzamide C(sp^2)–H bond-functionalization reactions. Benzamide **1** C–H functionalization with alkynes and carbon monoxide, as well as aminoquinoline benzamide **1** homocoupling proceeds via the Co(I)/Co(III) catalytic cycle. Accordingly, oxidation of Co(II) salt in the presence of benzamide **1**, followed by C–H bond activation forms Co(III) aryl complex **12**. Next, coordination of the C–H bond-functionalization partner (alkyne or CO) takes place to form complex **13**, which undergoes a migratory insertion step to yield Co(III) complex **14**. Product **15** forms after the reductive elimination step, where Co(I) species are liberated and then reoxidized to Co(II) and returned to the catalytic cycle (Scheme 6).[11b] In turn, benzamide **1** C–H bond functionalization reactions with alkenes and amines proceed via the Co(II)/Co(IV) catalytic cycle and involve an oxidatively in-



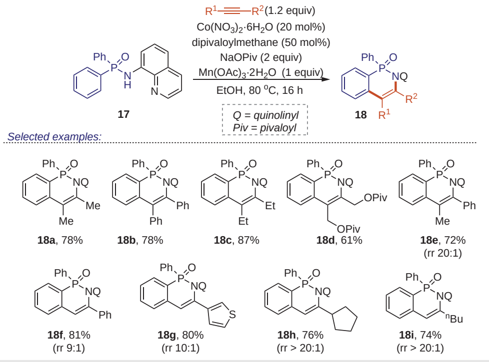
Scheme 6 The catalytic cycle of cobalt-catalyzed, 8-aminoquinoline-directed benzamide **1** C(sp^2)–H bond functionalization

duced reductive elimination (ORE) pathway. Consequently, the beginning of the catalytic cycle to Co(III) aryl complex **14** is the same. But then Co(III) aryl complex **14** is oxidized to Co(IV) species **16**, which undergoes rapid reductive elimination to yield product **15** and liberate Co(II) species that can return to the catalytic cycle (Scheme 6).[11b]

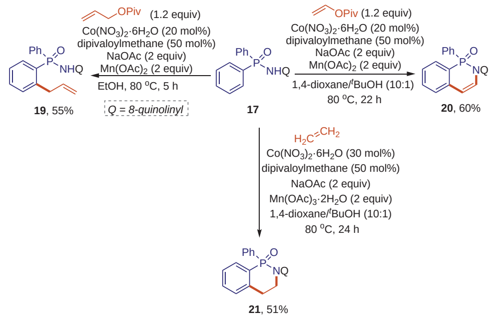
4 C(sp^2)–H Bond Functionalization of 8-Aminoquinoline Phosphinamides

In 2016, we published a study showing that phosphinic amides **17** are excellent substrates for cobalt-catalyzed C(sp^2)–H bond functionalization with alkynes and olefins. Phosphinic amide **17** reactions with alkynes proceeded in the presence of *in situ* formed Co(II)dipivaloylmethane as the catalyst, NaOPiv as the base, and Mn(III) acetate as the oxidant in ethanol (Scheme 7).[13] The C–H functionalization using unsymmetrical internal and terminal alkynes under the found reaction conditions allowed to obtain cyclic products **18** with good overall yields (up to 87%) and good to excellent regioselectivities (9/1 to >20/1).

Furthermore, we demonstrated that phosphinic amides **17** are competent substrates for C–H bond functionalization with olefins (Scheme 8).[13] For example, C–H functionalization reaction with allyl pivalate under slightly modified reaction conditions yielded the allylation product **19** in 55% yield. However, phosphinic amide **17** reaction with vinyl pivalate formed cyclic product **20** in 60% yield. Phosphinic amide **17** C–H annulation took place also in the reaction with ethylene forming **21** in 51% yield.



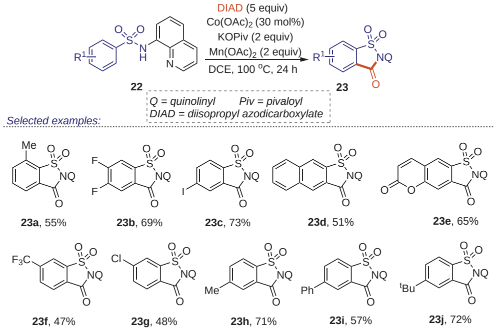
Scheme 7 Cobalt-catalyzed, 8-aminoquinoline-directed C–H annulation of phosphinic amides **17** with alkynes



Scheme 8 Cobalt-catalyzed, 8-aminoquinoline-directed phosphinic amide **17** C–H bond functionalization with alkenes

5 C(sp^2)–H Bond Carbonylation of 8-Aminoquinoline Sulfonamides

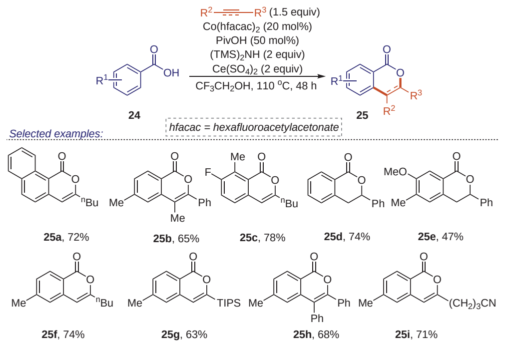
We found that not only aminoquinoline benzamides **1**, but also aminoquinoline sulfonamides **22** are applicable for cobalt-catalyzed C–H bond carbonylation giving efficient access to various saccharin derivatives **23**. The reactions proceeded in the presence of Co(II) acetate as the catalyst, Mn(OAc)$_2$ as the co-oxidant, and employed DIAD as a carbon monoxide source (Scheme 9).[14]



Scheme 9 Cobalt-catalyzed, 8-aminoquinoline-directed C–H bond carbonylation of sulfonamides **22**

6 C–H Bond Functionalization of Benzoic Acids

Success with the development of cobalt-catalyzed, aminoquinoline-directed C(sp^2)–H bond activation and functionalization methodology led us to investigate other functionalities that could be used as directing groups under cobalt catalysis. Gratifyingly, we found that a weakly coordinating carboxylate group can direct C(sp^2)–H bond activation and functionalization under cobalt catalysis. The synthetic potential of this methodology was demonstrated by reacting benzoic acids **24** with various terminal and internal alkynes to yield the corresponding isocoumarin derivatives **25a–c**,**f–i** (Scheme 10).[15] The main advantage of the discovered method is the use of native functionality as a directing group, thus avoiding at least two reaction steps involving the installation and removal of the directing group. Additionally, we demonstrated that optimized reaction conditions are also suitable for benzoic acid **24** *ortho*-C(sp^2)–H bond functionalization with alkenes allowing access to 3,4-dihydroisocoumarin derivatives **25d**,**e** (Scheme 10).

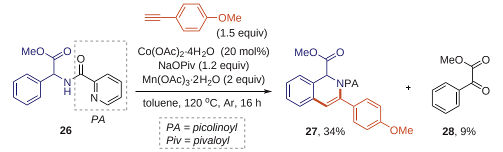


Scheme 10 Cobalt-catalyzed C–H bond annulation of benzoic acid **24** with alkynes and alkenes

7 C(sp^2)–H Bond Functionalization of Phenylglycine Derivatives

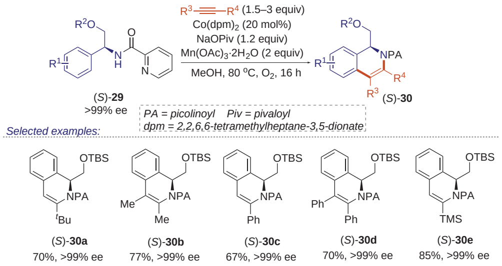
When Liene Grigorjeva moved back to the Latvian Institute of Organic Synthesis, our group focused the research on the C–H bond functionalization of amino acid derivatives. Amino acids have wide application as molecular scaffolds for drug development and these are essential building blocks for bioactive peptides and protein engineering. However, the synthesis of unnatural amino acids typically relies on multistep reactions with low cost-efficiency.[16] Moreover, natural amino acids are excellent substrates for the C–H bond functionalization considering wide availability and low cost.

We were interested to study whether phenylglycine could be an efficient substrate for cobalt-catalyzed C–H bond activation and could undergo C–H bond functionalization with alkynes. As a model substrate we chose phenylglycine picolinamide derivative **26**, Co(II) acetate as the catalyst, NaOPiv as the base, and Mn(III) acetate as the reaction oxidant (Scheme 11).[17] However, we discovered that, besides the formation of desired product **27**, α-keto ester **28** was formed in significant amounts. The formation of α-keto ester **28** could be explained by the oxidation of the substrate amino group, followed by hydrolysis, and that clearly indicated the instability of substrate **26** under the reaction conditions.



Scheme 11 Cobalt-catalyzed, picolinamide-directed C–H bond annulation of phenylglycine derivatives **26** with alkynes

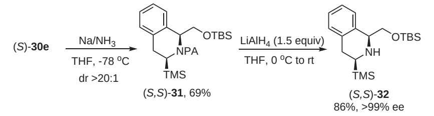
To overcome this problem, we decided to modify phenylglycine substrates to phenylglycinols, thus potentially reducing the reactivity of substrate α-position and making substrates more stable towards cobalt catalysis. We confirmed our concept and disclosed a novel method for the cobalt-catalyzed C–H bond annulation of phenylglycinol derivatives **29** (Scheme 12).[18] We were pleased to find that a broad substrate scope was tolerated under the reaction conditions, which consisted of a variety of terminal and internal alkynes as well as different substituents in the benzene ring moiety and led to the large diversity of dihydroisoquinolines **30** with yields up to 85%. Moreover, the stereochemical integrity of amine α-position was fully preserved during the reaction, and no loss of enantiopurity was observed.



Scheme 12 Cobalt-catalyzed, picolinamide-directed C–H annulation of phenylglycinol derivatives **29** with alkynes

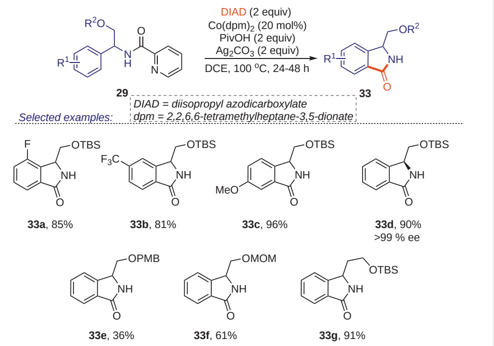
Additionally, we were able to reduce the double bond of the product (*S*)-**30e** in a highly diastereoselective fashion (d.r. > 20/1) and subsequently remove the picolinamide directing group to access highly substituted enantiopure tetrahydroisoquinoline derivative (*S*,*S*)-**32** (Scheme 13).[18]

In the same year, we extended our study and reported a method for cobalt-catalyzed C–H bond carbonylation of



Scheme 13 Synthesis of tetrahydroisoquinoline (*S*,*S*)-**32**

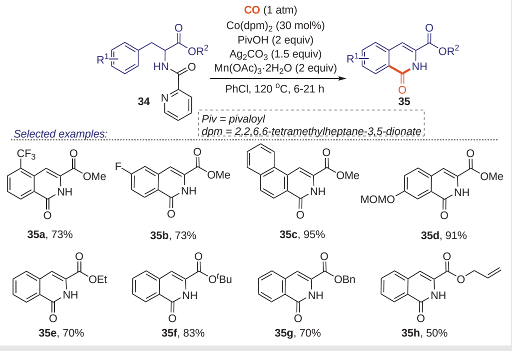
phenylglycinol derivatives **29** using DIAD as a CO surrogate (Scheme 14).[19] Interestingly, under optimized reaction conditions picolinamide served as a traceless directing group,[20] whereas in our previous annulation reports this was not observed. The optimized reaction conditions involved Co(II) dipivaloylmethane as the catalyst, pivalic acid as the additive, and Ag$_2$CO$_3$ as the reaction oxidant. We demonstrated a broad substrate tolerance with product yields of up to 96%, excellent regioselectivity, and full retention of the original stereochemistry.



Scheme 14 Cobalt-catalyzed, picolinamide-directed C–H carbonylation of phenylglycinol derivatives **29** with DIAD as the carbon monoxide source

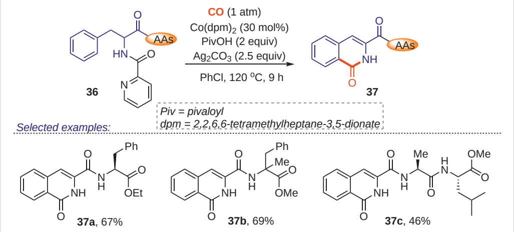
8 C(sp^2)–H Bond Functionalization of Phenylalanine Derivatives

In 2021, we switched our attention to the C(sp^2)–H bond activation and functionalization of phenylalanine derivatives **34** and developed a novel method for the synthesis of 1,2-dihydroisoquinolinolones **35** via cobalt-catalyzed C–H bond carbonylation with carbon monoxide (Scheme 15).[21]



Scheme 15 Cobalt-catalyzed, picolinamide-directed C–H carbonylation of phenylalanine derivatives **34** with carbon monoxide

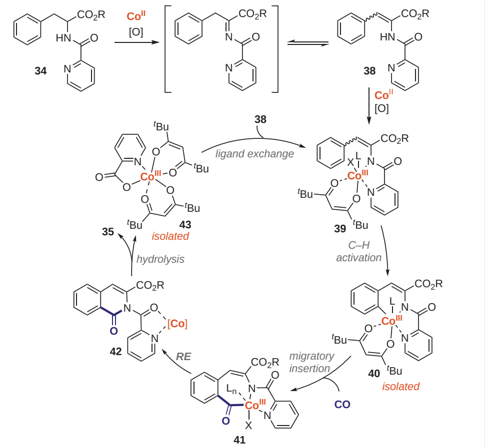
Additionally, in this transformation we also observed the removal of the picolinamide directing group *in situ*. The developed method exhibits a wide substrate scope, including substrates containing halide, alkyl, ether, and trifluoromethyl groups as well as heterocycles. Encouraged by these results, we applied the method for more challenging substrates – short peptides **36** (Scheme 16).[21] Although a slight modification of the reaction conditions was necessary, the corresponding carbonylation products **37** were obtained with up to 69% yield. Unfortunately, a partial peptide racemization was observed (up to 93% ee).



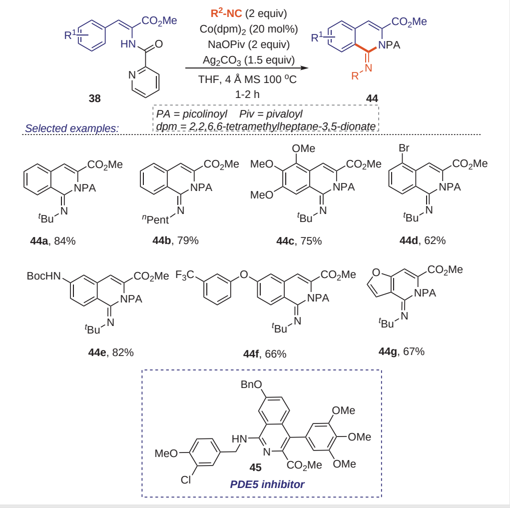
Scheme 16 Cobalt-catalyzed, picolinamide-directed C–H bond carbonylation of short peptides **36**

We performed detailed mechanistic studies and confirmed that initially an unsaturated phenylalanine intermediate **38** is formed via the SET mechanism (Scheme 17). First, in the presence of unsaturated substrate **38** Co(II) is oxidized to form Co(III) complex **39**, which further undergoes C–H bond cobaltation to form C–H activated Co(III) intermediate **40**, which was isolated and fully characterized by NMR data and XRD analysis. After CO migratory insertion, reductive elimination takes place to form compound **42**, which is then hydrolyzed to liberate product **35** and Co(III) complex **43**. We isolated Co(III) complex **43** and confirmed its catalytic activity for carbonylation reaction. The catalytic cycle restarts with ligand exchange in complex **43** to form intermediate **39**.[21]

As a continuation of our previous work on C(sp^2)–H bond functionalization of phenylalanine derivatives, in 2022 we reported a protocol for the synthesis of iminoisoquinolines **44** via cobalt-catalyzed C–H bond imination of α-amidoacrylates **38** using isocyanides (Scheme 18).[22] The developed method allowed to use a wide substrate scope with various isocyanides and α-amidoacrylates **38** yielding dihydroisoquinolines **44** in good to excellent yields (up to 84%). Despite that the picolinamide directing group was not cleaved under the reaction conditions *in situ*, it could be readily removed under reductive conditions using LiAlH$_4$ or Zn/AcOH. In addition, the reported method was used as the



Scheme 17 Plausible mechanism for cobalt-catalyzed, picolinamide-directed C(sp^2)–H bond carbonylation of phenylalanine derivatives **34**

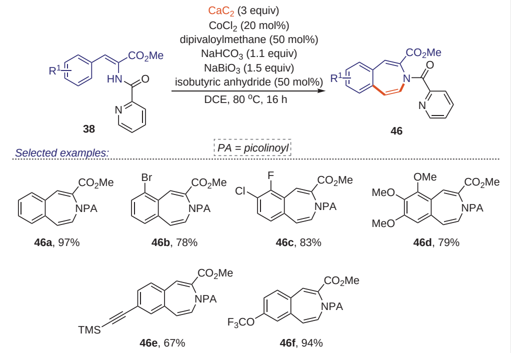


Scheme 18 Cobalt-catalyzed, picolinamide-directed C(sp^2)–H bond imination of α-amidoacrylates **38**

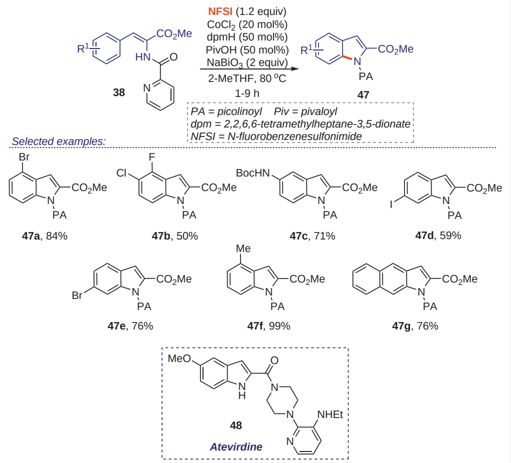
key step for the synthesis of PDE5 inhibitor **45** containing an amino isoquinoline core.

Recently, we reported a study on the picolinamide-directed C–H bond annulation reaction of α-amidoacrylates **38** under cobalt catalysis using CaC$_2$ as the acetylene source (Scheme 19).[23] The developed method overcomes limitations of the use of acetylene gas by substituting it with efficient, solid, and easy-to-handle calcium carbide. During optimization studies we found that the use of *in situ* prepared Co(dpm)$_2$ as the catalyst, NaHCO$_3$ as the base, isobutyric anhydride as the additive, and NaBiO$_3$ as the oxidant was crucial for the successful transformation. A variety of electron-poor and electron-rich α-amidoacrylates **38** were well-tolerated under the reaction conditions, however, heterocyclic substrates gave only a trace amount of the desired products **46**. The catalytic cycle for this transformation is similar to the previously reported Co(III)/Co(I) cycle (Scheme 17). We determined that water required for the generation of acetylene gas is released from the reagents used and the reaction solvent.

Another interesting study we published was the intramolecular amidation reaction for the synthesis of indole-2-carboxylates. In this case, picolinamide was used as a di-



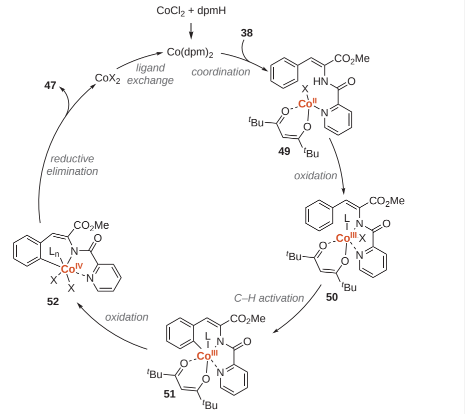
Scheme 19 Cobalt-catalyzed, picolinamide-directed C(sp^2)–H bond annulation with CaC$_2$ as the acetylene source



Scheme 20 Cobalt-catalyzed, picolinamide-directed intramolecular amidation of α-amidoacrylates **38**

recting group in combination with *in situ* prepared $Co(dpm)_2$ as the catalyst, PivOH as the additive, and $NaBiO_3$ as the reaction oxidant. We found that *ortho*-, *meta*-, and *para*-substituted α-amidoacrylates **38** bearing electron-withdrawing as well as electron-donating groups reacted smoothly giving products **47** in moderate to excellent yields (Scheme 20).[24] To demonstrate the utility of the developed methodology, we applied it to the synthesis of the anti-HIV drug atevirdine (**48**).

Based on DFT studies, cyclic voltammetry studies, and control experiments, we proposed the plausible reaction mechanism (Scheme 21).[24]



Scheme 21 The plausible catalytic cycle for cobalt-catalyzed intramolecular amidation of α-amidoacrylates **38**

First, the active $Co(dpm)_2$ catalyst is formed *in situ* from $CoCl_2$ and dipivaloylmethane ligand. After coordination/oxidation sequence the C–H bond activation takes place to form cobaltacycle **51**. Then NFSI oxidizes Co(III) intermediate **51** to high-valent aryl-Co(IV) species **52**, which undergoes oxidatively induced reductive elimination to deliver the desired product **47** and returns Co(II) species to the catalytic cycle. Ligand exchange restarts the catalytic cycle.

9 Conclusion

This Account shows our contribution over a decade to the development of new methods using cobalt-catalyzed C–H bond activation and functionalization approach as well as mechanistic studies. It highlights the concept that involves the use of simple cobalt(II) salts in combination with bidentate chelation assistance as high-valent cobalt precursors. We have demonstrated that this approach is a powerful tool for the construction of different types of heterocyclic compounds, including isoquinolinones, phthalimides, saccharines, isoindolinones, benzazepines, indoles, etc., with a potential application in medicinal chemistry. Since the development of this concept, numerous research groups have made great efforts to develop more sustainable synthetic protocols with an aim to reduce or eliminate current shortcomings, such as the use of directing groups that are unable or difficult to cleave, the use of stoichiometric amounts of metal-based oxidants, solvent waste, etc. Consequently, more sustainable synthetic protocols have been developed lately, for example by using native substrate functionalities as directing groups or exploiting modern alternatives to transition-metal-based oxidants including photoredox and electrochemical methods or using eco-friendly solvents. We believe that in the near future synthetic methods that will combine several sustainability aspects will be developed thus to be useful not only for fundamental, but applied research as well. We hope that this minireview will inspire further developments in this field.

Conflict of Interest

The authors declare no conflict of interest.

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Cobalt-Catalyzed C−H Annulation of Aryl Sulfonamides and Benzamides with CaC_2 as the Acetylene Source

Aleksandrs Cizikovs and Liene Grigorjeva*

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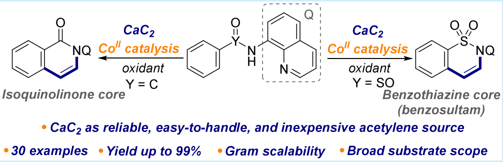
ABSTRACT: We have developed a cobalt-catalyzed, aminoquinoline-directed C−H/N−H annulation reaction of benzamides and aryl sulfonamides, enabling access to 3,4-unsubstituted isoquinolinone and 3,4-unsubstituted benzothiazine dioxide derivatives. This method employs calcium carbide as an inexpensive, easy-to-handle, and solid acetylene source. The reaction conditions showed a broad functional group tolerance, which allowed the synthesis of various C−H/C−N annulation products in yields of up to 99%.

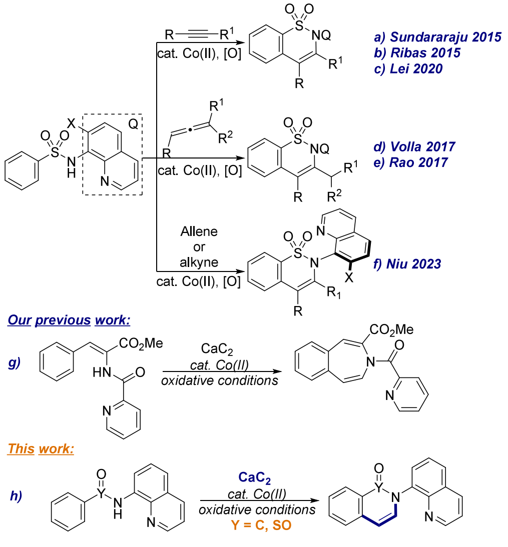


Calcium carbide is an inexpensive and solid reagent that reacts with water to produce acetylene and is considered to be one of the most effective surrogates for gaseous acetylene.[1] Compared to gaseous acetylene, CaC_2 has several advantages, such as being less risky to transport and not requiring complicated high-pressure equipment, and generally it is safer and more convenient to handle. The use of CaC_2 in organic synthesis has therefore gained much attention as it allows sustainable production of a variety of valuable organic compounds, including heterocycles.[2]

Recently, we have shown that CaC_2 can also be used as the acetylene source in a transition metal-catalyzed C−H bond functionalization reaction.[3] Transition metal-catalyzed C−H bond activation and functionalization is a valuable tool for the construction of target molecules.[4] Today, it is possible to use cheaper, less toxic and more environmentally friendly first row transition metal (Fe, Co, Ni, etc.) catalysts for the C−H bond activation and functionalization as an alternative to the typically employed noble metal catalysts (Ir, Rh, Pd, etc.).[5] In this context, cobalt(II) salt catalysts in combination with bidentate directing groups have received significant attention and since the initial report by Daugulis group in 2014,[6] many valuable methods based on this approach have been developed.[7] Several research groups have successfully applied this approach to the synthesis of benzosultams (Scheme 1, a-f),[8] which are a subclass of bicyclic sulfonamides and are found in many biologically active molecules, pharmaceuticals and agrochemicals.[9]

In 2015, Sundararaju[8a] and Ribas[8b] (Scheme 1, a,b) independently published the first examples on cobalt-catalyzed sulfonamide C−H annulation with alkynes. Later, Lei's group described the same method using electricity as the sole oxidant (Scheme 1, c).[8c] In 2017, Volla[8d] and Rao[8e] independently reported cobalt-catalyzed sulfonamide reactions with allenes (Scheme 1, d,e). Impressive studies on enantioselective annulation of aryl sulfonamides were carried out by Niu and colleagues (Scheme 1, f).[8f]

Scheme 1. Cobalt-Catalyzed C(sp^2)−H Bond Annulation with CaC_2 as the Acetylene Source



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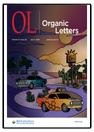

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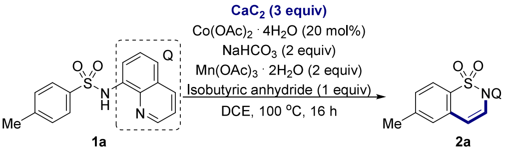
Org. Lett. 2025, 27, 7070−7074

Despite the notable progress achieved during the past decade in sulfonamide C−H bond annulation reactions, the methodology lacks examples of unsubstituted benzosultams at C3/C4 positions. Very recently, our group developed a novel approach for the synthesis of 3-benzazepines through cobalt-catalyzed, picolinamide-directed C−H bond annulation with acetylene using CaC_2 as the acetylene source (Scheme 1, g).[3] Inspired by these results, we envisioned that sulfonamides would react similarly to α-amidoacrylates with CaC_2 to give unsubstituted benzosultams under cobalt catalysis.

Herein we report the first example of efficient C3/C4 unsubstituted benzosultam synthesis through cobalt-catalyzed aminoquinoline-directed C(sp^2)−H bond annulation, using CaC_2 as the acetylene gas source.

For the optimization studies we used *p*-toluenesulfonamide **1a** as the model substrate and commercially available CaC_2, which was additionally grounded to a powder consistency (Table 1).[10]

Table 1. Optimization of the Reaction Conditions[a]



entry	change from the conditions above	yield, %[b]
1	$Co(dpm)_2$ instead of $Co(OAc)_2{\cdot}4H_2O$	38
2	$CoCl_2$ instead of $Co(OAc)_2{\cdot}4H_2O$	81
3	None	92
4	LiOPiv instead of $NaHCO_3$	90
5	NaOPiv instead of $NaHCO_3$	77
6	NaH_2PO_4 instead of $NaHCO_3$	74
7	TEA instead of $NaHCO_3$	trace
8	PivOH instead of $NaHCO_3$	80
9	Ac_2O instead of isobutyric anhydride	86
10	$(Piv)_2O$ instead of isobutyric anhydride	75
11	w/o isobutyric anhydride	68
12	$NaBiO_3$ instead of $Mn(OAc)_3{\cdot}2H_2O$	82
13	$Mn(OAc)_2/O_2$ instead of $Mn(OAc)_3{\cdot}2H_2O$	79
14	MeCN instead of DCE	trace
15	TFE instead of DCE	trace
16	*t*-BuOAc instead of DCE	71

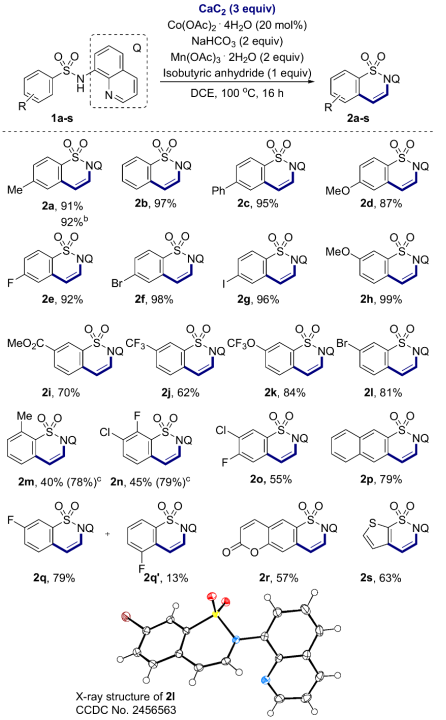
[a] Reaction conditions: **1a** (0.1 mmol), CaC_2 (3 equiv), $NaHCO_3$ (2 equiv), $Co(OAc)_2{\cdot}4H_2O$ (20 mol %), $Mn(OAc)_3{\cdot}2H_2O$ (2 equiv), isobutyric anhydride (1 equiv), DCE (1 mL), 100 °C, 16 h. [b] NMR yield using iodoform as an internal standard.

We were pleased to find that, by employing a similar catalytic system that showed good reactivity in our previous studies on α-amidoacrylate annulations with calcium carbide,[3] we could observe the formation of corresponding benzosultam derivative **2a** in 38% yield (Table 1, entry 1). Catalyst screening (entries 1−3) revealed that the yield of **2a** can be increased to 92% using $Co(OAc)_2{\cdot}4H_2O$ as the reaction catalyst. Changing the $NaHCO_3$ additive to other base additives, such as LiOPiv, NaOPiv or NaH_2PO_4, had a slight impact on the product **2a** yield (entries 4−6), while the triethylamine base was not suitable for the reaction (entry 7). In addition, pivalic acid as an additive was found to be similarly effective, as the formation of benzosultam **2a** was observed in an 80% yield (entry 8). Substitution of isobutyric anhydride with acetic anhydride (entry 9) or pivalic anhydride (entry 10) led to a slight decrease in the yield of product **2a** to 86% and 75% respectively. However, in the absence of isobutyric anhydride, the yield of the product decreased to 68% (entry 11). Our previous studies as well as literature examples suggest that isobutyric anhydride most likely is the ligand for metallacyclic intermediates.[3] Interestingly, other oxidants such as $NaBiO_3$ (entry 12), which was proven to be effective in our previous studies on the synthesis of 3-benzazepines[3] or indole-2-carboxylates,[11] or Mn(II) acetate in combination with O_2 (entry 13) showed equally good results and provided product **2a** in 79% and 82% yield. Using MeCN or TFE (entries 14−15) as the reaction solvent, we observed only a product trace, which indicates that, similarly to the reaction with triethylamine additive (entry 7), they can act as good ligands that can coordinate to the catalyst and reduce the activity of the catalyst or completely deactivate it. We observed that also *t*-BuOAc solvent did not improve the product **2a** yield (entry 16). Furthermore, it is worth mentioning that in the control experiment without the cobalt catalyst formation of benzosultam **2a** was not observed, and without the Mn(III) oxidant the desired product **2a** was obtained in only 8% yield.[10]

After optimization of the reaction conditions, we turned our attention to examination of the substrate scope for substituted sulfonamides **1a**−**s** with different functional groups (Scheme 2). We observed that the benzenesulfonamides **1a**−**1s** with *ortho*, *meta-,* and *para*-substitution patterns underwent the annulation reaction smoothly, giving the corresponding products **2a**−**s** generally with acceptable to excellent yields (40−99%). Diverse functionalities were tolerated under the optimized reaction conditions. The reaction of substrate **1a** bearing methyl functionality or unsubstituted benzenesulfonamide **1b** with CaC_2 gave products **2a** and **2b** in great yields, 91% and 97%. Moreover, upscaling the reaction to the gram scale gave product **2a** in 92% yield, suggesting that the reaction could be easily scalable. Halogenated sulfonamide derivatives **1e**, **1f**, **1g** and **1l** and dihalogenated substrates **1n** and **1o** gave the corresponding benzosultams **2n** and **2o** in moderate to great yields (up to 98%). It is noteworthy that the *meta*-substituted products **2h**−**2l** were obtained in good to excellent yields (62−99%) as single regioisomers. The structure of product **2l** was unambiguously established by a single-crystal X-ray study (Scheme 2). In turn, we found that 3-fluoro benzenesulfonamide **1q** was a competent substrate for annulation with CaC_2, but in this case the reaction was not selective and both regioisomers **2q** (79%) and **2q′** (13%) were isolated.[12] Sterically hindered *ortho*-substituted sulfonamides **1m** and **1n** gave the corresponding products **2m** and **2n** in moderate yields of 40% and 45% respectively; the reduced reaction yields arose from the poor reactivity of the starting materials. We demonstrated that 2-naphtalenyl sulfonamide **1p** is also reactive under the reaction conditions, affording naphthosultam **2p** in 79% yield as a single regioisomer. Pleasingly, heterocyclic sulfonamides **1r** and **1s** were also compatible with the reaction conditions affording products **2r,s** in good yields.

Inspired by the result that sulfonamides **1** were successfully annulated with calcium carbide as the source of acetylene gas, we decided to apply this method also to benzamide substrates **3**. We were pleased to find that product formation was observed under standard reaction conditions, and no further

Scheme 2. Substrate Scope with Respect to Sulfonamides[a]

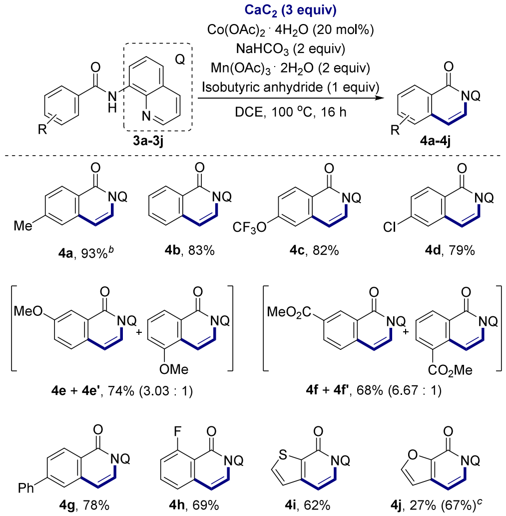


[a]Reaction conditions: **1** (0.5 mmol), CaC_2 (1.5 mmol, 3 equiv), $Co(OAc)_2{\cdot}4H_2O$ (0.1 mmol, 20 mol %), $NaHCO_3$ (1.0 mmol, 2 equiv), $Mn(OAc)_3{\cdot}2H_2O$ (1.0 mmol, 2 equiv), isobutyric anhydride (0.5 mmol, 1 equiv), DCE (5 mL), 100 °C, 16 h, isolated yields. [b]Standard conditions, starting from 1 g (3.35 mmol) **1a**. [c]brsm (based on recovered starting material).

optimization of the reaction conditions was necessary (Scheme 3).

We found that different functional groups were tolerant of the reaction conditions. Benzamides **3** containing electron donating groups (products **4a**, **4g**), electron withdrawing groups (product **4c**), and electroneutral and halogenated benzamides (products **4b**, **4d**) underwent the annulation reaction and gave the desired products in very good to high yields (78–93%). Unfortunately, under the reaction conditions, the *meta*-substituted benzamides **3** containing methoxy or methyl ester functionalities produced an inseparable mixture of both regioisomers. However, the regioisomer ratios were acceptable and the overall yields of products **4e** and **4f** were 74% and 68% respectively. In contrast to benzosultams **1m,n**, the *ortho*-substituted product **4h** was formed in good yield—69%. In addition, two heterocyclic amides **3i,j** were subjected to C−H bond functionalization with CaC_2. As a result, thienopyridinone **4i** was obtained in a good yield of 62%, while furopyridinone **4j** was isolated in only 27% yield. We found that in this case the low yield is due to the low conversion of the starting material. Taking into account the recovered starting material, the product yield was 67%.

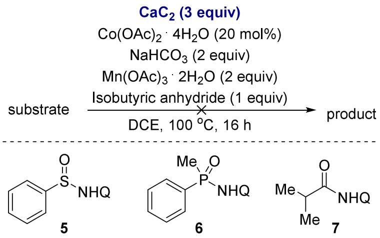
Scheme 3. Substrate Scope with Respect to Benzamides[a]



[a]Reaction conditions: **3a−j** (0.5 mmol), CaC_2 (1.5 mmol, 3 equiv), $Co(OAc)_2{\cdot}4H_2O$ (0.1 mmol, 20 mol %), $NaHCO_3$ (1.0 mmol, 2 equiv), $Mn(OAc)_3{\cdot}2H_2O$ (1.0 mmol, 2 equiv), isobutyric anhydride (0.5 mmol, 1 equiv), DCE (5 mL), 100 °C, 16 h, isolated yields. [b]Standard conditions, starting from 500 mg (1.91 mmol) **3a**. [c]brsm (based on recovered starting material).

While studying the scope of the developed method, we found some limitations (Scheme 4). Substrates such as sulfinamide **5** or phosphinic amide **6** did not withstand the reaction conditions, and only traces of the desired products along with a large amount of degradation byproducts were detected. On the other hand, isobutyramide 7 was found to be unreactive under the reaction conditions, which could be explained by the fact that harsher reaction conditions are required for activation and functionalization of the C(sp^3)−H bond.

Scheme 4. Unsuccessful Substrates[a]

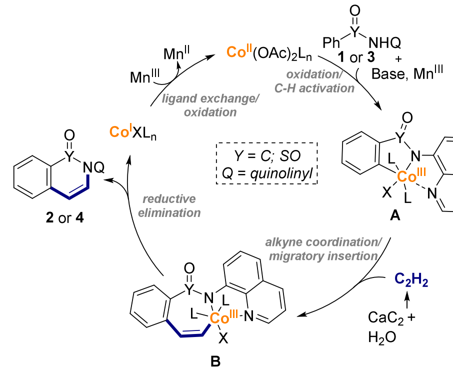


[a]Reaction conditions: substrate **5−7** (0.1 mmol), CaC_2 (3 equiv), $NaHCO_3$ (2 equiv), $Co(OAc)_2{\cdot}4H_2O$ (20 mol %), isobutyric anhydride (1 equiv), $Mn(OAc)_3{\cdot}2H_2O$ (2 equiv), DCE (1 mL), 100 °C, 16 h. NMR yield was determined using iodoform as an internal standard.

It has recently been reported and discussed in detail that two types of catalytic cycles are possible for aminoquinoline-directed cobalt-catalyzed C−H bond functionalizations.[13]

Thus, based on the relevant literature examples[8,14] and previous reports from our group,[3,11,15] it is highly unlikely that a catalytic cycle involving Co(IV) species is operative in our case. Therefore, we propose a plausible reaction pathway via the Co(I)/Co(III) catalytic cycle (Scheme 5). It should be noted that acetylene is produced *in situ* by slow-release mode from CaC_2 and a proton source arising from reagents, solvent and moisture.[16]

Scheme 5. Plausible Reaction Mechanism



Initially, the Co(II) catalyst coordinates to sulfonamide **1** or benzamide **3**, and after a sequence of oxidation/C−H bond activation, five-membered cobaltacycle **A** is formed. Subsequently, coordination and migratory insertion of acetylene formed *in situ* from the reaction of calcium carbide with proton source provides intermediate **B**. It is possible that complex **A** undergoes ligand exchange to replace acetate to isobutyrate ligand prior to the migratory insertion step.[3] Next, after reductive elimination, the final product **2** or **4** is released together with the Co(I) species, which is then reoxidized with $Mn(OAc)_3{\cdot}2H_2O$ to restart the catalytic cycle.

In summary, we have developed an efficient protocol for the synthesis of cyclic sulfonamides and isoquinolinones using cobalt-catalyzed, aminoquinoline-directed $C(sp^2)$−H bond annulation with calcium carbide as the acetylene source. This strategy features broad substrate tolerance encompassing various functionalities, including alkyl, aryl, alkoxy, and ester as well as halogens. We proved that the reaction is scalable, as the reaction on the gram scale gave the product with a similar yield. We propose that the reaction proceeds via a Co(I)/Co(III) catalytic cycle.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c01981.

> Experimental procedures, complete optimization table, and characterization data for all new compounds along with copies of the NMR spectra. (PDF)

Accession Codes

Deposition Number 2456563 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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Aleksandrs Čižikovs dzimis 1998. gadā Rīgā. Latvijas Universitātē (LU) ieguvis dabaszinātņu bakalaura (2020) un dabaszinātņu maģistra (2022; ar izcilību) grādu ķīmijā, par maģistra darbu saņēmis Latvijas Zinātņu akadēmijas (LZA) Mārtiņa Straumaņa un Alfrēda Ieviņa vārdbalvu ķīmijā. Ir pētījuma "Jauna metode indolu iegūšanai, izmantojot kobalta katalīzi", kas ierindots nozīmīgo 2024. gada sasniegumu skaitā, līdzautors, par šo pētījumu saņēmis LZA prezidenta Atzinības rakstu.
Patlaban strādā Latvijas Organiskās sintēzes institūta Organiskās sintēzes metodoloģijas grupā. Galvenais pētījuma mērķis ir jaunu C-H saites funkcionalizēšanas metodoloģiju izstrāde, izmantojot lētus kobalta sāļus kā reakciju katalizatorus. Sešu oriģinālpublikāciju, četru apskatrakstu un vienas grāmatas nodaļas līdzautors.

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