Supporting Information

Resolving a Reactive Organometallic Intermediate from Dynamic Directing Group Systems by Selective C–H Activation

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Supporting information

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GENERAL METHODS AND MATERIALS

All chemicals were purchased from commercial suppliers with the highest available purity. Chemicals were used as received, except liquid aldehydes and 1-octene which were distilled under anhydrous conditions prior to use and stored under N2. The reactions using air or moisture sensitive compounds were carried out with oven-dried glassware under an atmosphere of Ar or N2. Molecular sieves 4 Å were pre-activated by heating to 600 °C under reduced pressure for 15 min followed by extended storage at 150 °C. Anhydrous solvents were passed through alumina columns in a Glass Contour solvent dispensing system and stored over molecular sieves, with the exception of acetonitrile and acetic acid which were dried through fractional distillation (atmospheric pressure) over appropriate drying agent and stored over 3 Å MS. p-Toluenesulfonic acid was dried by heating to 70 °C under high vacuum for 30 min. MnCl2 and NiBr2 were dried by heating to 50 °C under high vacuum, followed by storage in a vacuum desiccator. Toluene and toluene-d8 were deoxygenated by purging with a stream of dry N2 gas for 30 min. CDC13 was filtered through a plug of anhydrous K2CO3 to remove acidic impurities, followed by drying over activated 4 Å MS under inert atmosphere. Solvents for workup, extractions and flash column chromatography were of analytical grade and used as supplied. Thin layer chromatography was carried out using pre-coated Merck silica gel 60 F254 aluminum-backed plates (0.25 mm), visualized by UV light (λ = 254 nm) followed by staining in a solution of phosphomolybdic acid in ethanol. Flash column chromatography was carried out using Merck silica gel 60 (0.040-0.063 mm). NMR spectroscopy was carried out using Bruker Avance DMX 500 and Ascend 400 spectrometers. Chemical shifts are reported as δ values (ppm) with (residual) solvent as internal standard.

EXPERIMENTAL PROCEDURES

Scheme S1. Dynamic systemic resolution of directing group system investigated.

Generation of dynamic directing group system

To a dry Schlenk tube under N2 were added imine A1 (24.3 mg, 0.135 mmol), followed by anhydrous, deoxygenated toluene (2.43 mL). Next, aromatic amines 2-amino-3-methylpyridine (2, 6.8 μL, 7.3 mg, 0.0675 mmol), o-anisidine (3, 7.6 μL, 8.3 mg, 0.0675 mmol), 2-fluoroaniline (4, 6.5 μL, 7.5 mg, 0.0675 mmol), 2-methylthioaniline (5, 8.5 μL, 9.4 mg, 0.0675 mmol), 2-aminothiophenol (6, 8.0 mg, 0.0675 mmol) and 8-aminoquinoline (7, 9.7 mg, 0.0675 mmol) were added in succession under N2. Finally, a stock solution of acid/s in anhydrous, deoxygenated toluene (0.27 mL, total acid concentration 0.1 M) was added and the reaction mixture was heated to 80 °C for 1 h, after which an equilibrium point was reached according to 1H-NMR analysis.
Resolution of dynamic directing group system
Rh(PPh₃)₃Cl (13.9 mg, 0.015 mmol) and ground, pre-activated 4 Å MS (20 mg) were added to a dry 1.5 mL vial and left at room temperature under high vacuum for several hours. Afterwards, a dynamic directing group system was generated as described above, and part of the homogenous yellow solution was withdrawn (0.60 mL, corresponding to 0.015 mmol of each amine 2-7, 0.030 mmol of A1) and directly added to the incubated metal/MS mixture via syringe under Ar. The vial was immediately heated to 80 °C and the reaction mixture was stirred heavily under Ar. A gradual color change of the reaction mixture from deep red to yellow could be observed if the resolution proceeded efficiently. The reaction was analyzed by sampling of an aliquot (100 μL) into CDCl₃ (0.50 mL with added phenyltrimethylsilane as internal standard), filtering of the resulting mixture through a pad of celite and analysis by ¹H-NMR spectroscopy. At room temperature, the composition of the diluted reaction sample was stable over more than 24 h.

Iterative deconvolution experiments
For each deconvolution experiment, a dynamic directing group system was initially generated as described above. Next, the appropriate metals (0.015 mmol each) were added together to a dry 1.5 mL vial with ground, pre-activated 4 Å MS (20 mg) and dried under high vacuum for several hours. Finally, resolution was accomplished as described above, and all samples were analyzed after 30 and 60 min with phenyltrimethylsilane as internal standard. All experiments yielding product were performed in duplicate (Table S1).

Table S1. Deconvolution data after 30 min.

| Entry | Metals | Acids | c_p (mM) | Entry | Metals | Acids | c_p (mM) | Entry | Metals | Acids | c_p (mM) |
|-------|--------|-------|----------|-------|--------|-------|----------|-------|--------|-------|----------|
| 1     | M1-M4  | B1-B4 | 0.0      | 7     | M5-M6  | B1, B2| 0.0      | 13    | M7     | B1    | 0.0      |
| 2     | M1-M4  | B5-B8 | 0.0      | 8     | M5-M6  | B3, B4| 0.0      | 14    | M7     | B2    | 0.0      |
| 3     | M5-M8  | B1-B4 | 3.8      | 9     | M7-M8  | B1, B2| 7.1      | 15    | M8     | B1    | 2.6      |
| 4     | M5-M8  | B1-B4 | 4.0      | 10    | M7-M8  | B1, B2| 5.1      | 16    | M8     | B1    | 1.7      |
| 5     | M5-M8  | B5-B8 | 1.8      | 11    | M7, M8 | B3, B4| 5.4      | 17    | M8     | B2    | 6.5      |
| 6     | M5-M8  | B5-B8 | 1.7      | 12    | M7, M8 | B3, B4| 2.9      | 18    | M8     | B2    | 6.6      |

One-pot imine formation and C-H activation protocol
To a dry Schlenk tube under N₂, were added benzaldeyde (41.2 μL, 43.0 mg, 0.405 mmol) and activated 4 Å MS (ca 1000 mg). Anhydrous deoxygenated toluene (2.43 mL) was added, followed by successive addition of aniline (1, 6.2 μL, 6.3 mg, 0.0675 mmol), 2-amino-3-methylpyridine (2, 6.8 μL, 7.3 mg, 0.0675 mmol), 3-anisidine (3, 7.6 μL, 8.3 mg, 0.0675 mmol), 2-fluoroaniline (4, 6.5 μL, 7.5 mg, 0.0675 mmol), 2-methylthioaniline (5, 8.5 μL, 9.4 mg, 0.0675 mmol), 2-amino-benzenitriile (6, 8.0 mg, 0.0675 mmol) and 8-aminquinoline (7, 9.7 mg, 0.0675 mmol) under N₂. Finally, a stock solution of benzoic acid in anhydrous, deoxygenated toluene (0.27 mL, 0.1 M) was added and the reaction mixture was heated to 80 °C for 24 h. After that time, NMR analysis confirmed that all seven imines had formed and that ca 97% of the initial aldehyde was cleanly converted to imines. From this mixture, resolution and analysis was performed as described above.

Reaction monitoring by ESI-MS
After the dynamic system had been generated, resolution was conducted with Rh(PPh₃)₃Cl (13.9 mg, 0.015 mmol) and ground, pre-activated 4 Å MS (20 mg) according to the description above for 30 min. After this time, an aliquot (100 μL) was withdrawn, diluted with CDCl₃ (0.50 mL), filtered through a plug of celite and analyzed by ¹H-NMR spectroscopy with phenyltrimethylsilane as internal standard. Ca 30% yield of the organometallic complex P2 had been obtained under these conditions. Next, an aliquot of the NMR sample (2.0 μL) was withdrawn, diluted with MS-grade MeOH (2.0 mL), filtered through an acrodisc and immediately injected in the ESI-MS. Under all conditions tested (varying capillary voltage, injection temperature etc.) the major peak in the positive mode spectrum was a sharp peak at 823.20 m/z, corresponding to P2 with loss of chlorine. The isotopic distribution pattern also fully corresponded to the expected rhodacyle. The instrument could be further tuned to detect what we tentatively attribute to be cationic [P2-H⁺] at 857.87 m/z. However, control experiments with pure P2 almost exclusively yielded the peak of the dechlorinated cationic complex at 823.20 m/z together with further fragmentation products, indicating that the stability of the [P2-H⁺] and [P2+H⁺] is quite low under MS.

Figure S1. ESI-MS spectrum of dynamic system.
conditions. Likewise, we tried searching for complexes belonging to potential P3-P7 adducts along with their dechlorinated analogues. A very small peak at 877.07 m/z could potentially be attributed to a C-H activated intermediate [P3+[H]] or a [A3−RhCl(PPh3)2+[H]] complex, but no other peaks belonging to any other C-H activation product could be identified (Figure S1). No detectable decomposition occurred in the MS sample over 5 h.

**Reaction analysis by **$^{31}$P- and $^1$H-NMR spectroscopy

A dynamic system was first generated as described above, only with deoxygenated, dry toluene-$d_8$ as the solvent instead of toluene. Resolution was then conducted with Rh(PPh$_3$)$_3$Cl (13.9 mg, 0.015 mmol) and ground, pre-activated 4 Å MS (20 mg) for 30 min. After this time, an aliquot (0.6 mL) of the reaction mixture was withdrawn and filtered through a plug of celite directly into an NMR tube. NMR spectrometric analysis was conducted within 5 min (Figure S2-S3). The sample exhibited full stability at room temperature over 24 h, after which time only minor changes in the $^1$H-NMR spectrum could be recorded. Deconvolution of the components was conducted by dissolving A1 and benzoic acid in toluene-$d_8$ in an NMR tube, followed by addition of one amine at a time, shaking of the mixture for 1 h at 80 °C and consequent measurement of the $^1$H-NMR spectrum to determine the peak positions of each newly formed imine.

**Investigation of DSR time course**

A dynamic systemic resolution was set up as described in previous sections (cf. Scheme S1), scaled up 1.7 times (1.0 mL solution). The reaction was heated at 80 °C and monitored by withdrawal of aliquots (100 μL), which were diluted into CDCl$_3$ (0.5 mL) with added phenyltrimethylsilane as internal standard. The obtained time course for compound P2 is displayed in Figure S4. After 4 h, all of compound P2 had decomposed to unidentified side products.

**Effects of system size and composition**

Systems from imine A1 (0.03 mmol) and amines 2-9 (0.015 mmol each), present or absent as indicated in Table S2, were generated in toluene (0.60 mL) in the presence of benzoic acid (3.0 μmol) at 80 °C under Ar for 1 h. To these systems, Rh(PPh$_3$)$_3$Cl (0.015 mmol), and 4 Å MS (ground, 20 mg), were added and the reactions were allowed to proceed at 80 °C for 1 h. The yields were determined by $^1$H-NMR spectroscopy with PhSiMe$_3$ as internal standard.
**Table S2. Effect of size and composition of dynamic imine system on resolution efficiency**[^1]  

![Diagram](image)

| 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Yield P2 (%) |
|---|---|---|---|---|---|---|---|-------------|
| √ | × | × | × | × | × | × | × | 73 |
| √ | √ | × | × | × | × | × | × | 57 |
| √ | × | × | × | × | × | √ | × | 27 |
| √ | √ | × | × | × | × | × | × | 32 |
| √ | √ | × | × | × | × | × | × | 15 |

[^1]: Presence (checkmark) or absence (cross) of specified amine in dynamic system.

**Incompatible metals and ligands**

Beside the metals tested in the iterative deconvolution experiments, some additional potential catalysts were evaluated. Pd[^4^]-based catalysts do not give rise to metal hydrides (only palladacyclic dimeric species) but are still potent catalysts for C-H activation. Pd(OAc)[$_2$] was however not compatible with the screening conditions and resulted in decomposition. All other tested Pd[^3^] species were tolerated by the screening conditions, i.e. C-H activation with the dynamic system described in Scheme S1 occurred with Rh(PPh[$_3$])[Cl] even in the presence of 1 equiv. of Pd[^3^] species. Co[^1^] was not compatible with the system, and induced decomposition into the reactions when tested. Finally, once Rh(PPh[$_3$])[Cl] had been deemed the best metal complex for C-H activation, other ligands where also tested. Monovalent ligand P(ο-Tol)[$_3$] was compatible with the screening conditions, while multidentate ligands such as dppe and xanthos were not tolerated and led to shutdown of all C-H activation activity.

**Synthesis of compounds A1, A2, P1, and P-ket**

**(E)-N,1-diphenylmethanimine (A1)**[^6^]. To a dry round-bottom flask with pre-activated 4 Å MS (whole beads, 10 g) were added anhydrous CH$_2$Cl$_2$ (100 mL) and benzaldehyde (1.02 mL, 1.06 g, 10.0 mmol), followed by dropwise addition of aniline (0.91 mL, 0.93 g, 10.0 mmol). The resulting solution was stirred slowly at r.t. under N$_2$ for 20 h, at which point the reaction was finished according to NMR analysis. The reaction mixture was filtered through a pad of celite, washed with anhydrous CH$_2$Cl$_2$ and concentrated in vacuo to yield a yellow solid. Further purification by recrystallization from hexane yielded the product as yellow crystals (1.34 g, 7.4 mmol, 74% yield).[^10^] $^1$H NMR (500 MHz, CDCl$_3$), δ$_H$ = 8.47 (s, 1H), 7.92 (dd, J = 6.6, 2.7 Hz, 2H), 7.48 (dd, J = 7.2, 3.5 Hz, 3H), 7.40 (t, J = 7.8 Hz, 2H), 7.23 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$), δ$_C$ = 160.3, 152.1, 136.2, 131.3, 129.1, 128.77, 128.72 (partial overlap), 125.9, 120.8.

**(E)-N-(3-methylpyridin-2-yl)-1-phenylmethanimine (A2)**[^8^]. To a dry round-bottom flask equipped with a Dean-Stark apparatus were added anhydrous toluene (50 mL) and benzaldehyde (508 μL, 531 mg, 5.0 mmol) and 2-amino-3-methylpyridine (504 μL, 541 mg, 5.0 mmol). The yellow solution was heated to reflux for 14 h. The resulting yellow solution was concentrated in vacuo, and the obtained oil was further purified by Kugelrohr distillation of the remaining starting material. The pure product was obtained as a yellow oil that solidified over time (524 mg, 2.65 mmol, 53% yield). $^1$H NMR (500 MHz, CDCl$_3$), δ$_H$ = 9.07 (s, 1H), 8.31 (d, J = 4.4 Hz, 1H), 8.08 – 7.94 (m, 2H), 7.55 (d, J = 7.2 Hz, 1H), 7.51 – 7.46 (m, 3H), 7.09 (dd, J = 7.4, 4.8 Hz, 1H), 2.47 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$), δ$_C$ = 161.6, 159.5, 146.1, 138.8, 136.3, 131.6, 129.4, 128.74, 128.67 (partial overlap), 121.8, 17.4.

[**RhCl{(2-benzylidene-3-methylpyridine)-PPh[3]_3}** (P2)][^1^]. To a dry Schlenk tube was added Wilkinson’s catalyst (194.3 mg, 0.21 mmol) and ground 4 Å MS (200 mg). The solids were dried under vacuum at 80 °C for 30 min. The Schlenk tube was refilled with Ar and imine A2 (39.3 mg, 0.20 mmol) in anhydrous toluene (4 mL) was added. The mixture was stirred at 80 °C for 30 min, after which the entire reaction solution was directly applied to a patch of silica gel and rinsed through repeatedly with CH$_2$Cl$_2$. Finally, the product fraction was eluted with CH$_2$Cl$_2$/EtOAc 19:1, and concentrated to yield the product as a golden solid (142.0 mg, 0.17 mmol, 83% yield). $^1$H NMR (500 MHz, CDCl$_3$), δ$_H$ = 8.40 (d, J = 4.5 Hz, 1H), 7.66 (d, J = 7.7 Hz, 2H), 7.47 – 7.40 (m, 12H), 7.29 (d, J = 7.6 Hz, 2H), 7.16 – 7.03 (m, 18H), 6.88 (t, J = 7.2 Hz, 1H), 6.68 (t, J = 7.7 Hz, 2H), 6.52 (t, J = 5.6 Hz, 1H), 2.50 (s, 3H), -11.15 (q, J = 11.7 Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$), δ$_C$ = 227.8 (dt, J = 32.5, 7.8 Hz), 165.0, 146.3, 142.5, 137.8, 134.3 (t, J = 5.7 Hz), 132.4 (t, J = 23.1 Hz), 132.1 (d, J = 10.0 Hz), 129.2, 128.7, 128.2, 127.3 (t, J = 4.8 Hz), 126.0, 118.8, 18.9; $^{31}$P NMR (202 MHz, CDCl$_3$), δ$_P$ = 32.5 (d, J = 116 Hz).
1-phenylnonan-1-one (P-ket)$^3$. Compound P2 (42.1 mg, 0.049 mmol) was added to a dry 0.5 mL microwave tube and dissolved in anhydrous toluene (0.16 mL) under Ar. 1-Octene (39.2 μL, 28.1 mg, 0.25 mmol) was added dropwise via syringe, and the resulting red solution was capped, sealed and stirred under Ar for 24 h. The reaction mixture was allowed to cool to r.t. under inert atmosphere, after which the reaction mixture was mixed with MeCN (1.4 mL) and 1.0 M aq. HCl solution (1.4 mL). The mixture was stirred vigorously for 1 h at r.t. Afterwards, the yellow solution was extracted with EtOAc (4 × 2 mL), and the combined organic phases were dried with MgSO$_4$, filtered and concentrated. Further purification by column chromatography (9:1 hexane/EtOAc) yielded the pure product as a colorless oil (8.6 mg, 0.039 mmol, 80% yield). $^1$H NMR (400 MHz, CDCl$_3$), $\delta_{H} = 8.00 - 7.90$ (m, 1H), 7.55 (t, $J = 7.3$ Hz, 1H), 7.46 (t, $J = 7.6$ Hz, 1H), 2.96 (t, $J = 7.4$ Hz, 1H), 1.78 - 1.68 (quin, $J = 7.3$ Hz, 1H), 1.40-1.25 (m, 70H), 0.88 (t, $J = 6.8$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$), $\delta_{C} =$ 200.6, 137.1, 132.8, 128.5, 128.0, 38.6, 31.8, 29.43, 29.38, 29.2, 24.4, 22.6, 14.1.

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