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

Fredrik Schaufelberger,[a] Brian J.J. Timmer,[a] and Olof Ramström*[a][b]

Abstract: Catalyst discovery from systems of potential precursors is a challenging endeavor. Herein, a new strategy applying dynamic chemistry to the identification of catalyst precursors from C-H activation of imines is proposed and evaluated. Using hydroacylation of imines as a model reaction, the selection of an organometallic reactive intermediate from a dynamic imine system, involving many potential directing group/metal entities, is demonstrated. The identity of the amplified reaction intermediate with the best directing group could be resolved *in situ* via ESI-MS, and coupling of the procedure to an iterative deconvolution protocol generated a system with high screening efficiency.

Much effort in synthetic organic chemistry is dedicated to the search for new catalytic systems, often discovered through time-consuming single catalyst screening. To accelerate the discovery of novel catalysts, constitutional dynamic chemistry has emerged as a promising concept.[1] Reversible covalent bonds are in this case utilized to allow the thermodynamic or kinetic adaptation of dynamic systems in response to applied selection pressures, resulting in amplification of the systemic constituents that best adapt to the given settings. In principle, this approach of simultaneously generating and evaluating multiple catalysts in one-pot is ideal for abbreviating discovery times, and the requirement for all catalyst candidates to be synthesized, purified, characterized and evaluated individually is circumvented.[2] This concept has previously been explored by us,[3] and others,[4] showing that catalysts can be rapidly identified using dynamic deconvolution, self-resolved from dynamic systems, or amplified from binding to transition state analogues.

The direct identification of optimal catalyst-substrate species, which act as reactive intermediates in the catalyzed transformations, is in this context especially attractive. *In situ* detection of such intermediates, generated from dynamic systems involving many potential catalysts and substrates, thus provides information of the properties of the catalyst-substrate entity required for achieving catalytic activation.[2g, 5]

This challenge has been addressed in the present investigation, where we describe a dynamic chemistry strategy for efficient identification of a reactive metal-substrate intermediate. The approach relies on dynamic systemic resolution (DSR),[6] applying kinetically controlled resolution steps to thermodynamically controlled systems, targeting a metal-substrate complex that provides information as to which metal/substrate combination is able to efficiently initiate a catalytic cycle. Metals, acids and directing groups (DGs) were screened in a model system of selective C-H activation reactions by interruption of the catalytic cycle to amplify the reactive intermediate (**Figure 1**). This enabled *in situ* identification of the active complex with the corresponding directing group and metal using ESI-MS. We furthermore demonstrate the coupling of this method to an iterative deconvolution protocol to provide efficient screening of reaction parameters.

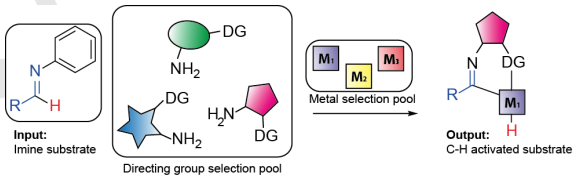

Figure 1. DG-based C-H activation of imines with metal catalyst.

DG-controlled C-H functionalization is a versatile and powerful strategy for synthesis of a range of complex molecular targets.[7] However, many studies have shown that even small changes in sterics or electronics of the DGs can lead to significant activity differences.[8] Also, the need to attach and detach the DG from the substrate constitutes a significant drawback. In the present study, it was hypothesized that transiently formed DGs based on dynamic covalent bonds can bypass such limitations,[9] enabling catalytic DGs with sufficiently rapid dynamic exchange processes.

Hydroacylation of aromatic imines with alkenes was chosen as a model reaction for the system,[10] projected to involve initial establishment of a transient DG via acid-catalyzed transimination.[11] The metal would subsequently coordinate to the DG and insert into the aldimine C-H bond via oxidative addition, generating a metal hydride intermediate. The rate-determining step in the catalytic cycle has been proposed to occur after the formation of the intermediate, enabling identification of this species in the process. This type of intermediate has also been observed with several different metals and DGs, for this and similar reactions, and was thus considered suitable for the proof-of-concept system.[12]

The overall hydroacylation process is outlined in **Figure 2**, indicating the imine exchange and the proposed detectable intermediate. In addition to being identifiable, the intermediate

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should also be compatible with the conditions of the dynamic process, including the different amines.

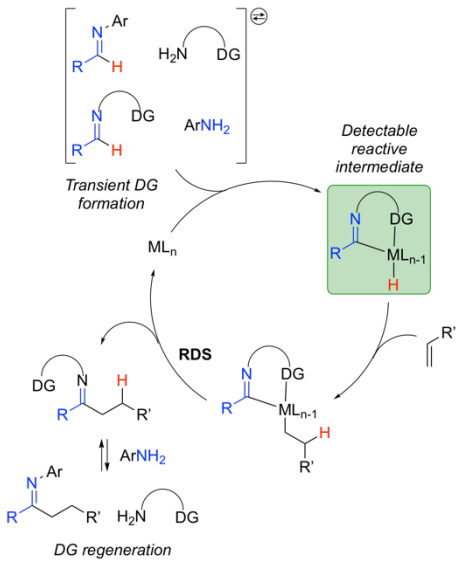

Figure 2. General scheme of dynamic directing group-controlled hydroacylation process.

To evaluate this, a dynamic imine system utilizing acid-catalyzed transimination was first constructed (**Figure 3**, top). Imine **A1** did not contain a functional DG, but all auxiliary amines **2**-**7** were selected to contain well-established DGs previously used for C-H functionalization processes.[8a, 9a, 13] Based on these structures, imines **A2**-**A7** formed transiently and under thermodynamic control in the dynamic system.

Next, the dynamic imine system was applied to a mixture of metals and acid co-catalysts to evaluate the feasibility of the DSR methodology. The use of mixtures of metals and additives in so-called "shotgun" approaches to catalyst screening have been explored, but well-working approaches towards structured deconvolution strategies of such mixtures have only recently been proposed.[2a, 14] In the present study, a multi-parameter, iterative deconvolution strategy was used.[2a] The investigated reagents, eight metal catalysts and eight acids (**Figure 3**), were divided into pools, which were evaluated pairwise, followed by selection of the best-performing combination and further division into smaller pools until a hit was found. The metals were selected to encompass both known, working catalysts (Ir^{I}, Rh^{I}, Pt^{0}, Ru^{II}) as well as controls (Mn^{II}, Zn^{II}, Ni^{II}, Cu^{I}).[12d, 12e, 15] Likewise, the acids were chosen to obtain a wide spread in pK_a, steric bulk and ability for complementary non-covalent interactions (cf. Supporting Information). For analysis, the expected hydride formation was targeted, since initial experiments following the consumption of the starting materials revealed that only this key product was formed. Thus, the large upfield NMR spectral shift of the imine proton upon transformation into a heavily shielded hydride (typical signals at 0 to -25 ppm), was followed.

The metals and acids were thus separated into pools of four, and the dynamic DG system was subjected to each metal/acid mixture (**Figure 3**). The alkene substrate was omitted to maximize amplification by preventing catalytic turnover. A short reaction time (30 min) at 80 °C in deoxygenated toluene, with added 4 Å MS to keep the system moisture-free, was found to produce a small amount of a new organometallic hydridic species, as evidenced by the appearance of a quartet at -11.2 ppm in the ^{1}H NMR spectrum (Round 1). No new major signals appeared in the indicative regions of the spectrum, other than amine-containing compound signal shifts due to metal complexation. The hydride peak could be observed in the two pools containing Ru, Rh, Ni and Ir. Furthermore, one acid combination proved slightly superior to the other, leading to the selection of this pool and dividing the metals and acids into four new pools each containing two species of each type (Round 2). From this round, the hydridic species could only be observed in pools with Rh and Ru. Further selection of the best acid combination and a final pool split (Round 3) allowed assignment of the key metal as Rh (**M7**) and the optimum acid as benzoic acid (**B2**). As a control, omitting the acid led to complete loss of activity in the system.

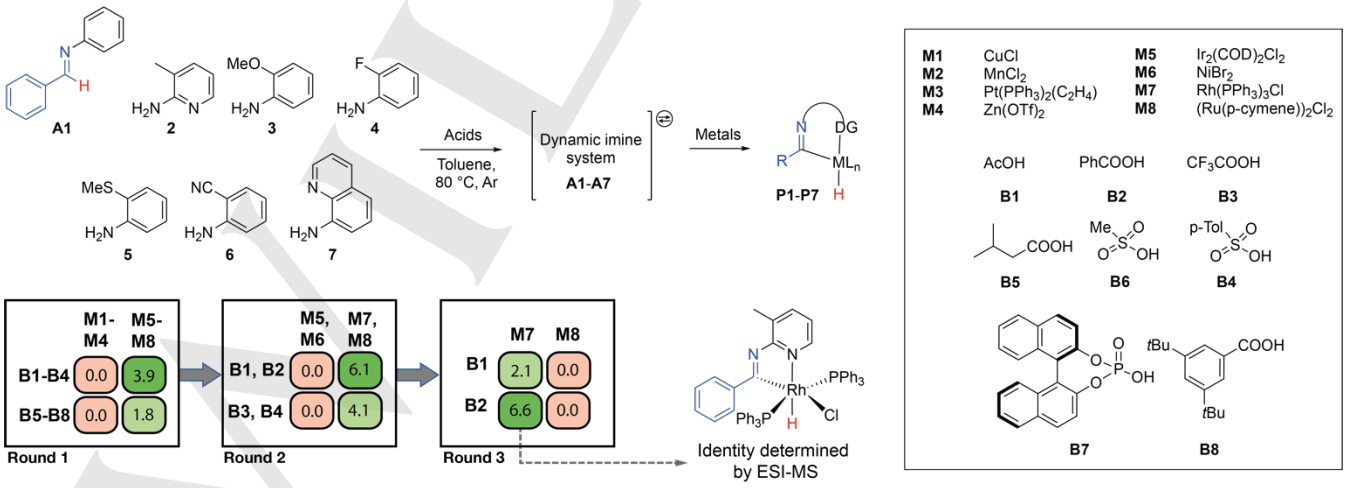

Figure 3. DSR of DG system with coupled iterative deconvolution. Numbers in boxes indicate concentration (mM, average values from duplicate experiments) of metal hydride species at -11.2 ppm. Concentrations determined by ^{1}H-NMR spectroscopy with $PhSiMe_3$ as internal standard. Conditions: Imine **A1** (0.03 mmol), amines **2**-**7** (0.015 mmol each), acids (3.0 µmol total), toluene (0.60 ml), 80 °C, Ar, 1 h, then metals (0.015 mmol each), 4 Å MS (20 mg), 80 °C, 30 min.

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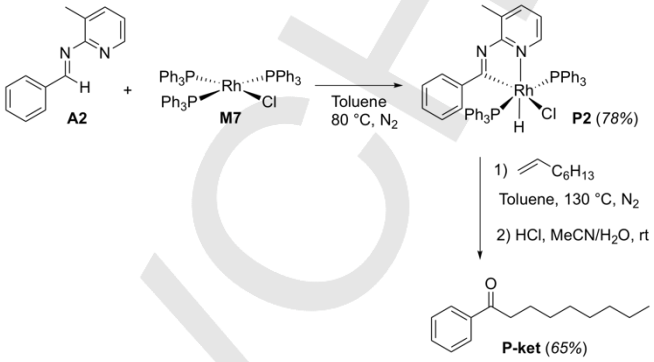
In view of the wealth of literature precedence, identification of the Rh species as the metal most proficient at performing the oxidative addition step of the hydroacylation process was unsurprising. Correspondingly, benzoic acid has also been utilized as a highly efficient co-catalyst in a number of Rh-catalyzed hydroacylations.[16]

Given that the organometallic intermediates have high molecular weights in comparison to the initial imines and DG-bearing amines, ESI-MS was selected as a straightforward methodology for identifying the key Rh-H containing species observable from the system. Indeed, direct monitoring of the reaction system involving species **B2**/**M7** with ESI-MS in positive mode allowed observation of the C-H activated product **P2** with a relatively strong [**P2**–H]$^+$ signal (Figure S1). Furthermore, an intense peak originating from the [**P2**–Cl]$^+$ signal could be observed. A very small concentration of potential product **P3** was otherwise the only additional organometallic intermediate observable.

Since the ESI-MS signals of C-H activated intermediates have the same mass as the unactivated metal-DG complexes, NMR spectroscopy was also employed for complementary qualitative analysis. Performing the reaction in toluene-d_8 allowed for more accurate ^{1}H- and ^{31}P-NMR analysis, indicating a process with relatively low amounts of side products despite the complexity of the system (Figures S2-S4). It was thus again evident that essentially only one single new species was formed, and this intermediate was assigned as product **P2**. These results show that coupling of the DSR process to an iterative deconvolution protocol allowed for efficient reaction parameter screening and *in situ* identification of the optimal DG, metal and acid for inducing oxidative addition. A total of 448 different reaction conditions were thus screened with just twelve reactions.

Although the system was capable of selectively resolving product **P2** in the presence of close structural analogues, higher concentrations of free amines were suspected to affect the resolution efficiency. ^{1}H-NMR monitoring of product **P2** over time indicated rapid C-H activation over the first 30 min, followed by a short plateau, before the reaction intermediate started to decompose (Figure S4). To test if the amine concentration was detrimental to product stability, the size of the dynamic imine system was increased and reduced by addition or removal of DG components (Table S2). This resulted in a clear correlation between total amine concentration and resolution efficiency.

Following these conclusions, a new approach to obtain higher efficiency was devised (**Scheme 1**). All relevant DG-containing free amines were thus condensed with slightly substoichiometric amounts of benzaldehyde with 4 Å MS to obtain a dynamic imine system with lower free amine content, yet retaining the dynamic properties of the exchange process. Indeed, C-H activation with $Rh(PPh_3)_3Cl$ from this system provided **P2** as the sole new product in a much-improved 81% yield over 30 min.



Scheme 2. Conversion of intermediate **P2** into hydroacylation product **P-ket**.

The presented selection strategy provided information on which metal/DG combinations were capable of inducing the oxidative addition step in the catalytic cycle. The overall hydroacylation reaction was therefore carried out using the selected intermediate to verify its function. It could thus be independently confirmed that the amplified organometallic species **P2** is indeed an intermediate for a hydroacylation reaction.[17] When compound **P2** was synthesized separately (**Scheme 2**), and treated with 1-octene in deoxygenated toluene at 130 °C, followed by hydrolysis with aqueous HCl, the expected ketone was obtained in good overall yield starting from imine **A2**.

In summary, we have demonstrated a new strategy applying dynamic chemistry to reactive organometallic intermediate discovery. A dynamic systemic resolution process could be used to amplify an intermediate in a catalytic cycle, and enabled direct identification of active metal/directing groups in a complex system. Furthermore, judicious coupling of this amplification method to an iterative deconvolution protocol led to powerful resolving efficiency in parameter space. The organometallic complex **P2** is by far the most intricate and reactive structure resolved from a dynamic system. This study thus additionally demonstrates that with appropriate optimization and choice of parameters, even transient or metastable species can be resolved from dynamic systems.

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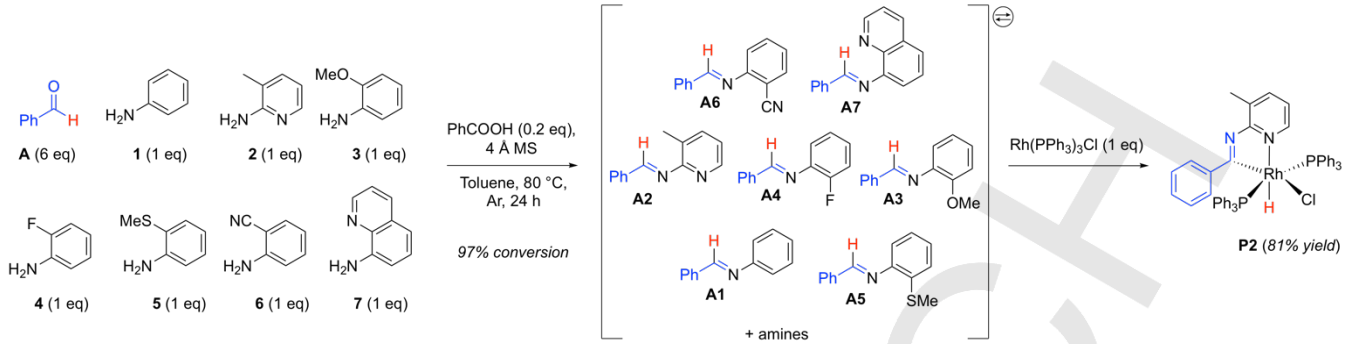

Scheme 1. Direct condensation followed by selective C-H activation of dynamic directing group system.

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Keywords: Dynamic chemistry • C-H activation • Catalysis • Directing group • Systems chemistry

[1] a) W. Zhang, *Dynamic Covalent Chemistry: Principles, Reactions and Applications*, John Wiley & Sons, Inc., Hoboken, NJ, **2017**; b) I. Azcune, I. Odriozola, *Eur. Polym. J.* **2016**, *84*, 147-160; c) R.-C. Brachvogel, M. von Delius, *Eur. J. Org. Chem.* **2016**, *2016*, 3662-3670; d) J.-M. Lehn, *Angew. Chem. Int. Ed.* **2015**, *54*, 3276-3289; e) Y. Jin, C. Yu, R. J. Denman, W. Zhang, *Chem. Soc. Rev.* **2013**, *42*, 6634-6654; f) A. Herrmann, *Chem. Soc. Rev.* **2014**, *43*, 1899-1933; g) L. Hu, F. Schaufelberger, B. J. J. Timmer, M. A. Flos, O. Ramström, in *Kirk-Othmer Encycl. Chem. Technol.*, John Wiley & Sons, Inc., Hoboken, NJ, USA, **2014**, pp. 1-25; h) M. C. Misuraca, E. Moulin, Y. Ruff, N. Giuseppone, *New J. Chem.* **2014**, *38*, 3336-3349; i) A. Wilson, G. Gasparini, S. Matile, *Chem. Soc. Rev.* **2014**, *43*, 1948-1962; j) P. Dydio, P.-A. R. Breuil, J. N. H. Reek, *Isr. J. Chem.* **2013**, *53*, 61-74; k) M. Barboiu, *Constitutional Dynamic Chemistry*, Springer Verlag, Berlin Heidelberg, **2012**; l) G. Gasparini, M. Dal Molin, L. J. Prins, *Eur. J. Org. Chem.* **2010**, *2010*, 2429-2440; m) B. L. Miller, *Dynamic Combinatorial Chemistry: In Drug Discovery, Bioorganic Chemistry, and Materials Science*, John Wiley & Sons, Inc., Hoboken, NJ, **2010**; n) J. N. H. Reek, S. Otto, *Dynamic Combinatorial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2010**.

[2] a) E. Wolf, E. Richmond, J. Moran, *Chem. Sci.* **2015**, *6*, 2501-2505; b) C. A. Muller, C. Markert, A. M. Teichert, A. Pfaltz, *Chem. Commun.* **2009**, 1607-1618; c) A. Hagemeyer, B. Jandeleit, Y. Liu, D. M. Poojary, H. W. Turner, A. F. Volpe Jr, W. Henry Weinberg, *Appl. Catal. A* **2001**, *221*, 23-43; d) M. T. Reetz, *Angew. Chem. Int. Ed.* **2001**, *40*, 284-310; e) R. F. Harris, A. J. Nation, G. T. Copeland, S. J. Miller, *J. Am. Chem. Soc.* **2000**, *122*, 11270-11271; f) M. B. Francis, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **1999**, *38*, 937-941; g) C. Hinderling, P. Chen, *Angew. Chem. Int. Ed.* **1999**, *38*, 2253-2256.

[3] a) F. Schaufelberger, O. Ramström, *J. Am. Chem. Soc.* **2016**, *138*, 7836-7839; b) F. Schaufelberger, O. Ramström, *Chem. Eur. J.* **2015**, *21*, 12735-12740.

[4] a) R. Kannappan, K. M. Nicholas, *ACS Comb. Sci.* **2013**, *15*, 90-100; b) G. Gasparini, L. J. Prins, P. Scrimin, *Angew. Chem. Int. Ed.* **2008**, *47*, 2475-2479; c) B. Brisig, J. K. M. Sanders, S. Otto, *Angew. Chem. Int. Ed.* **2003**, *42*, 1270-1273.

[5] a) M. N. Hopkinson, A. Gómez-Suárez, M. Teders, B. Sahoo, F. Glorius, *Angew. Chem. Int. Ed.* **2016**, *55*, 4361-4366; b) I. Fleischer, A. Pfaltz, *Chem. Eur. J.* **2010**, *16*, 95-99; c) J. Wassenaar, E. Jansen, Z.-J. van, F. M. Bickelhaupt, M. A. Siegler, A. L. Spek, J. Reek, N. H., *Nat. Chem.* **2010**, *2*, 417-421.

[6] a) L. Hu, Y. Zhang, O. Ramström, *Sci. Rep.* **2015**, *5*, 11065-11065; b) Y. Zhang, O. Ramström, *Chem. Eur. J.* **2014**, *20*, 3288-3291; c) L. Hu, O. Ramström, *Chem. Commun.* **2014**, *50*, 3792-3794; d) M. Sakulsombat, Y. Zhang, O. Ramström, *Top. Curr. Chem.* **2012**, *322*, 55-86; e) Y. Zhang, M. Angelin, R. Larsson, A. Albers, A. Simons, O. Ramström, *Chem. Commun.* **2010**, *46*, 8457-8459; f) P. Vongvilai, O. Ramström, *J. Am. Chem. Soc.* **2009**, *131*, 14419-14425; g) P. Vongvilai, M. Angelin, R. Larsson, O. Ramström, *Angew. Chem. Int. Ed.* **2007**, *46*, 948-950; h) R. Larsson, Z. Pei, O. Ramström, *Angew. Chem. Int. Ed.* **2004**, *43*, 3716-3718.

[7] a) J. Wencel-Delord, T. Droge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740-4761; b) T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 3362-3374; c) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879-2932.

[8] a) Y. Xu, G. Yan, Z. Ren, G. Dong, *Nat. Chem.* **2015**, *7*, 829-834; b) Y. Y. See, A. T. Herrmann, Y. Aihara, P. S. Baran, *J. Am. Chem. Soc.* **2015**, *137*, 13776-13779; c) D. P. Affron, O. A. Davis, J. A. Bull, *Org. Lett.* **2014**, *16*, 4956-4959.

[9] a) H. Sun, N. Guimond, Y. Huang, *Org. Biomol. Chem.* **2016**; b) F.-L. Zhang, K. Hong, T.-J. Li, H. Park, J.-Q. Yu, *Science* **2016**, *351*, 252-256.

[10] a) A. Ghosh, K. F. Johnson, K. L. Vickerman, J. A. Walker, L. M. Stanley, *Org. Chem. Front.* **2016**, *3*, 639-644; b) S. K. Murphy, V. M. Dong, *Chem. Commun.* **2014**, *50*, 13645-13649; c) C.-H. Jun, E.-A. Jo, J.-W. Park, *Eur. J. Org. Chem.* **2007**, *2007*, 1869-1881.

[11] a) J. Yang, Y. W. Seto, N. Yoshikai, *ACS Catal.* **2015**, *5*, 3054-3057; b) C.-H. Jun, J.-B. Hong, *Org. Lett.* **1999**, *1*, 887-889.

[12] a) F. Mo, G. Dong, *Science* **2014**, *345*, 68-72; b) P. Marcé, C. Godard, M. Feliz, X. Yáñez, C. Bo, S. Castillón, *Organometallics* **2009**, *28*, 2976-2985; c) D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 3645-3651; d) A. Ohtaka, N. Kato, H. Kurosawa, *Organometallics* **2002**, *21*, 5464-5466; e) A. Albinati, C. Arz, P. S. Pregosin, *J. Organomet. Chem.* **1987**, *335*, 379-394.

[13] L. D. Tran, O. Daugulis, *Angew. Chem. Int. Ed.* **2012**, *51*, 5188-5191.

[14] a) R. Bellini, S. H. Chikkali, G. Berthon-Gelloz, J. N. H. Reek, *Angew. Chem. Int. Ed.* **2011**, *50*, 7342-7345; b) D. W. Robbins, J. F. Hartwig, *Science* **2011**, *333*, 1423-1427; c) J. Wieland, B. Breit, *Nat. Chem.* **2010**, *2*, 832-837.

[15] B. Li, T. Roisnel, C. Darcel, P. H. Dixneuf, *Dalton Trans.* **2012**, *41*, 10934-10937.

[16] a) E.-A. Jo, C.-H. Jun, *Tetrahedron Lett.* **2009**, *50*, 3338-3340; b) C.-H. Jun, D.-Y. Lee, H. Lee, J.-B. Hong, *Angew. Chem. Int. Ed.* **2000**, *39*, 3070-3072.

[17] J. W. Suggs, *J. Am. Chem. Soc.* **1979**, *101*, 489-489.

10.1002/chem.201705273

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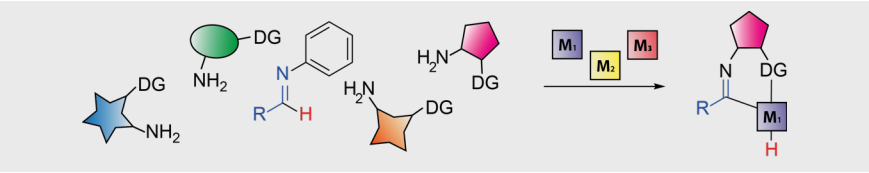

A new strategy applying dynamic chemistry to the selection of catalyst precursors from C-H activation of imines is presented. Using hydroacylation as a model reaction, the strategy enabled identification of an organometallic reactive intermediate from a dynamic imine system, where the best directing group could be resolved *in situ*.

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