Letter

Developing NHC-Iridium Catalysts for the Highly Efficient Enantioselective Intramolecular Hydroamination Reaction

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Developing NHC-Iridium Catalysts for the Highly Efficient Enantioselective Intramolecular Hydroamination Reaction.

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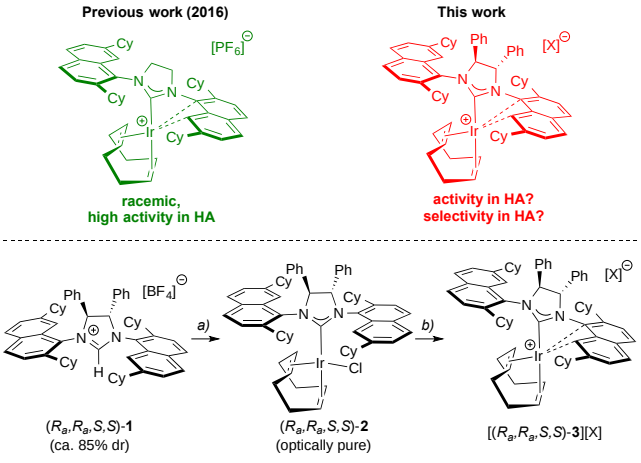
Supporting Information Placeholder

ABSTRACT: Chiral, cationic NHC-iridium complexes are introduced as catalysts for the intramolecular hydroamination reaction of unactivated aminoalkenes. The catalysts show high activity in the construction of pyrrolidines, which are accessed with excellent optical purity. Enantiomerically enriched piperidines and indolines are also produced and various functional groups are tolerated with this LTM system. A reaction mechanism is proposed and a major deactivation pathway of these catalysts is presented and discussed. **KEYWORDS:** *chiral NHC, iridium, catalysis, hydroamination, N-heterocycles*

Optically active *N*-heterocyclic compounds are of prime importance in commodity and specialty chemicals and are often present in natural products and medicines. One of the most elegant ways of producing compounds such as chiral pyrrolidines, piperidines or indolines is through the use of an enantioselective olefin hydroamination reaction starting from the appropriate aminoolefin precursor molecules.[1] Classical hydroamination (HA) reactions that employ electronically unbiased olefins and alkenes are also an illustration of perfect atom economy in chemical reactions, and although great progress has been achieved over the last two decades, they are far from well established. Advances since Marks' and coworkers first reports of asymmetric intramolecular HA reactions,[2] have by and large concentrated on developing the original rare-earth systems, alkali and alkaline earth metal catalysts as well as early-transition metal compounds.[1] Impressive recent results by the groups of Schafer,[3b] and Sadow,[3c-f] have indeed shown that chiral zirconium catalysts are able to provide pyrrolidine products with high enantiopurity and represent the current state of the art for these asymmetric transformations. The major drawback that remains with these catalyst systems is their highly sensitive nature and very limited functional group tolerance that impedes a broader implementation of this elegant synthetic methodology.

Late-transition metal (LTM) catalysts would without doubt alleviate the problem, but the asymmetric intramolecular HA reaction of unactivated aminoolefins has until now not been developed to any degree,[4] with a single report existing in the literature, in which Buchwald *et al.* use a cationic rhodium systems with chiral MOP-type ligands.[5]

In this context, we were inspired by results reported by Stradiotto *et al.* who have applied the dimeric $[Ir(COD)Cl]_2$ complex as a precatalyst in the non-chiral version of this reaction.[6] We were able to show that by replacing the halide with NHC structures featuring appropriately substituted naphthyl wingtips,[7] highly unsaturated, yet stable cationic $[(NHC)Ir(COD)]^+$ species can be isolated that display greatly improved activities in the intramolecular HA reaction (NHC = 2,7-SICyNap, Scheme 1, top left).[8] Unfortunately, a first foray into using an enantiopure NHC ligand led to highly attenuated catalyst activities and prevented an extended study.



a) 0.5 $[Ir(COD)Cl]_2$, NaO^{t}Bu, THF, work-up. *b)* Ag[X] or Na[X], CH_2Cl_2, work-up.

Scheme 1. Catalyst structures and synthesis of cationic 3[X] complexes.

Results herein report the preparation of optically pure $[(NHC)Ir(COD)]^+$ catalysts that combine the high activity of $[(2,7\text{-SICyNap})Ir(COD)]^+$ discussed above with excellent enantioselectivities in this HA reaction. Following

earlier studies from our group,[9] we installed enantiomerically pure (*S*,*S*)-diphenyldiamine into the NHC backbone in order to access the optically enriched (R_a,R_a)-isomer of the ligand salt (*ca.* 85% dr) containing the same unsymmetrically substituted 2,7-dicyclohexyl-1-naphthyl wingtips mentioned above.[10] This NHC salt (DiPh-2,7-SI-CyNap, **1**) was then used in the synthesis of neutral complex **2**, at which stage the minor stereoisomers of the NHC [(R_a,S_a),*S*,*S*)-**1**] and [(S_a,S_a),*S*,*S*)-**1**] were conveniently eliminated upon purification. Finally, salt metathesis with $AgPF_6$, $NaBArF_{24}$ or $AgNTf_2$ gave access to three cationic complexes (**3**[X]). All of these cationic, formally 14-electron complexes show a stabilizing interaction via one of the naphthyl groups, leading to tilting of the NHC structure as discussed elsewhere.[8]

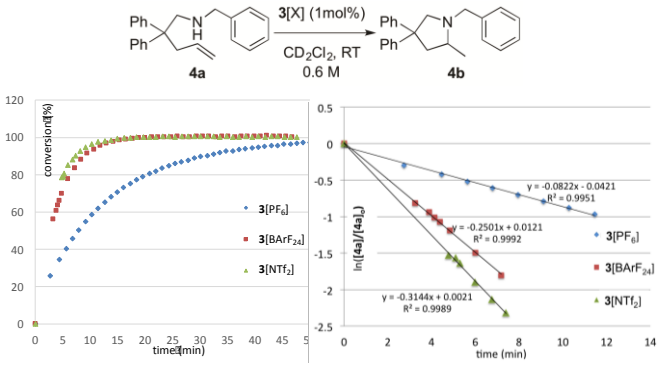
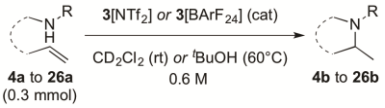


Figure 1. Plots of the conversion (%) *vs* time (min) for **4a** (left) and plots of ln([**4a**]/[**4a**]$_0$) *vs* time (min) (right).

The different anions were chosen in order to study the influence of the gegenion on the catalytic activity of these NHC-iridium species.[11] Figure 1 presents the outcome of this catalyst comparison as applied to the standard HA substrate *N*-benzyl-2,2-diphenylpent-4-en-1-amine (**4a**). Gratifyingly, all three catalysts showed excellent activities with full conversion achieved within one hour at room temperature employing comparatively low catalyst loadings for this challenging transformation (1 mol%). This corresponds to approximate TOF_{50} values of 377 h^{-1} {**3**[PF_6]}, 1071 h^{-1} for {**3**[$BArF_{24}$]} and 1500 h^{-1} for {**3**[NTf_2]}, placing these catalysts on par or above the most active HA catalysts reported (rare-earth systems).[2,3a,d] Enantioselectivities were equally satisfying and showed a slight dependence on the counteranion used, with **3**[$BArF_{24}$] providing marginally lower enantioselectivity (97% ee) than **3**[PF_6] (98.5% ee) and **3**[NTf_2] (99.5% ee). What came as a surprise was the fact that **3**[NTf_2] produced the most active system in this comparison. As far as we are aware, there is not a single report in the literature using a cationic iridium complex with an NTf_2 counteranion in catalysis.[12,13]

With these results in hand, we moved ahead and started a broader investigation into the substrate scope using both **3**[$BArF_{24}$] and **3**[NTf_2] catalysts and results are tabulated below (Table 1). Entry 4 shows that a switch to an alternative solvent (^{t}BuOH) also provides good results, but reactions in that case had to be run at slightly

Table 1: Scope of the intramolecular HA with 3[X].



Entry: **Product**	3[X]/mol%	Solvent	k_{obs}[a]	(Conv.)/ yield(%)[b]	ee(%)[c]
1: **4b** R=H	3[NTf_2]/1	CD_2Cl_2	31	(99)/95	>99
2: **4b** R=H	3[$BArF_{24}$]/1	CD_2Cl_2	25	(99)/93	97
3: **4b** R=H	3[PF_6]/1	CD_2Cl_2	8	(99)/96	99
4: **4b** R=H	3[$BArF_{24}$]/1	^{t}BuOH	-	94	97
5: **5b** R=4-NO_2	3[NTf_2]/2	CD_2Cl_2	20	(99)/92	98
6: **6b** R=4-Cl	3[NTf_2]/2	CD_2Cl_2	92	(99)/91	97
7: **7b** R=4-MeO	3[NTf_2]/2	CD_2Cl_2	49	(99)/95	98
8: **8b** R=4-CO_2Me	3[NTf_2]/2	CD_2Cl_2	53	(99)/94	>99
9: **9b** R=2-Me	3[NTf_2]/2	CD_2Cl_2	25	(99)/91	>99
10: **10b** R=CH_2Cy	3[NTf_2]/2	CD_2Cl_2	9	(99)/92	99
11: **11b** R=Me	3[NTf_2]/2	CD_2Cl_2	-[d]	(99)/89	90
12: **12b**	3[NTf_2]/2	CD_2Cl_2	2.2	(99)/96	97
13: **13b** R=H	3[NTf_2]/2	CD_2Cl_2	15	(99)/93	99
14: **14b** R=MeO	3[NTf_2]/2	CD_2Cl_2	1.7	(99)/96	96
15: **15b**	3[NTf_2]/5	CD_2Cl_2	30[d]	(89)/81	98
16: **16b**	3[NTf_2]/2	CD_2Cl_2	12	(99)/95	>99
17: **17b** R=H	3[NTf_2]/2	CD_2Cl_2	2.0	(99)/95	98
18: **18b** R=MeO	3[NTf_2]/2	CD_2Cl_2	1.5	(92)/88	96
19: **19b** R=H	3[NTf_2]/2	CD_2Cl_2	68	(99)/93[e]	97/99
20: **20b** R=Br	3[NTf_2]/2	CD_2Cl_2	75	(99)/92[e]	99/99
21: **21b** R=H	3[$BArF_{24}$]/5	CD_2Cl_2	18	(99)/90[e]	94/77
22: **22b** R=Br	3[NTf_2]/5	CD_2Cl_2	7	(99)/93[e]	96/76
23: **23b**	3[NTf_2]/2	CD_2Cl_2	3.3	(99)/94[e]	86/63
24: **24b**	3[$BArF_{24}$]/5	^{t}BuOH	-	93	87
25: **25b**	3[$BArF_{24}$]/7	^{t}BuOH	-	88	62

26: **26b**	**3**[NTf_2]/2	^{t}BuOH	-	92	94
27: **26b**	**3**[NTf_2]/5	CD_2Cl_2	0.7	(99)/91	90

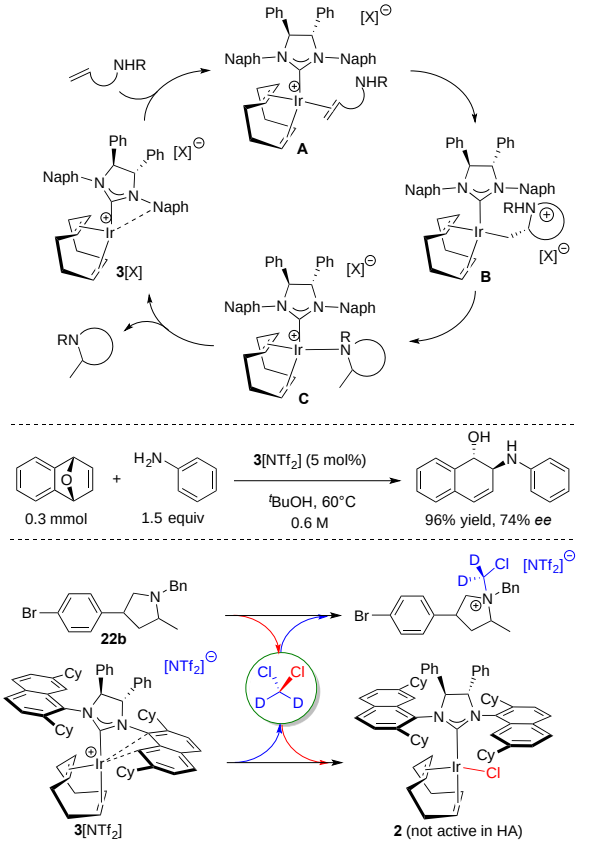
[a] (10^{-2} min^{-1}); pseudo-first-order rate constants, see SI for details. [b] Isolated yield. [c] Ee's determined by HPLC, by ^{1}H NMR of (*R*)-(−)-*O*-acetyl-mandelic acid derivatives or by ^{19}F NMR of Mosher amide derivatives. Absolute stereochemistry: (*S*) as deduced by comparison (**4b**, **9b**, **19b**, **20b**). [d] k_{obs} not given for **11** (reaction too fast); k_{obs} only indicative for **15**, see SI for details. [e] Diastereomeric ratios: 1.1:1 (**19b**, **20b**), 3:4 (**21b**), 1:1 (**22b**), 3:2 (**23b**). Isolated yields are for the mixture of diastereomers.

elevated temperature to ensure appropriate dissolution of the reaction mixture. Entries 5-11 highlight the fact that contrary to what had been recorded for rhodium,[6] the present system is relatively insensitive to variations of the nitrogen substituent. Different benzyl substitutions (entries 5-8), including ones that contain functional groups not tolerated by early-transition/lanthanide catalysts, uniformly lead to excellent results both in terms of reactivity and selectivity. Among the *para*-modified benzyl groups tested, we do not see any apparent trend between reactivity (k_{obs}) and their electronic nature. Replacing these benzyl groups with purely aliphatic substituents is equally successful (entries 10,11), although a slight erosion in enantioselectivity can be seen for the methyl substituted substrate **11a**. This might indicate that a more sterically encumbered *N*-substituent (entries 1-10) is beneficial for selectivity and is recognized by the catalyst structure. This is in line with the observation that the similarly sized *N*-phenyl substituent does not provide the corresponding product in optically enriched form (92% yield, 9% ee, see SI).[14]

3,3'-Substituted spirocyclic pyrrolidine products were accessed next and entries 12-16 show that here again, excellent reactivity produces the product molecules in very high optical purity. Noteworthy is the fact that the tosyl-protected substrate in entry 16 is perfectly amenable to undergo cyclization, again highlighting the functional group tolerance of the present LTM system. Unsymmetrically 2,2'-disubstituted substrates (entries 19,20) underwent cyclization to give diastereomer mixtures in approximately equal amount and with excellent enantioselectivity.

Kinetic resolution was also not observed in the case of racemic *N*-benzyl-2-phenyl-4-pentenamine or *N*-benzyl-2-isopropyl-4-pentenamine (entries 21-23), again giving rise to diastereomer mixtures in roughly equal amounts. Not surprisingly, reactivity was lower in these cases, but reactions could still be run at room temperature giving high yields of isolated product. The enantioselectivity of one of the diastereomers was consistently higher than that of the other. The most straightforward explanation of these results would see a scenario where the backbone substrate substitution is recognized by the catalyst structure, and where omitting it (H instead of R) would lead to a certain loss of enantioselection due to a less ordered transition state.

Gratifyingly, a 2,2'-difluoro substituted aminoalkene (**24a**, entry 24) was also amenable to cyclization to give the corresponding fluorinated pyrrolidine product in high yield and optical purity (93% yield, 87% ee). Such partially fluorinated pyrrolidines are of central importance in drug development,[15] and our results show how the asymmetric HA reaction might be used for accessing this family of compounds. Unfortunately, replacing the fluorine atoms by hydrogens and trying to ring-close the parent *N*-benzyl-pent-4-en-1-amine was not successful. While the intramolecular HA reaction did occur under forcing conditions (80 °C, 5 mol% cat.) to give acceptable yields of product (69%), the enantioselectivity of the transformation was negligible (20% ee). On the other hand, intramolecular HA to access an indoline derivative (**26b**) proceeded remarkably well and gave the product with excellent enantioselectivity and in high isolated yield (entries 26/27). Furthermore, a representative piperidine was also obtained with reasonable optical purity when employing a higher catalyst loading (entry 25).



Scheme 2. Proposed catalytic cycle (above), example of a ring-opening amination of oxabicycles catalyzed by 3[NTf_2] (middle) and catalyst decomposition in CD_2Cl_2 as observed for entry 22 of Table 1.

The proposed reaction mechanism is drawn in Scheme 2 (top) and involves coordination of the olefin (**A**) followed by external attack of the amine to give the neutral complex **B** before hydrogen migration generates cationic **C** that would regenerate **3**[X] after liberation of the product.[16] Overall, it would therefore follow a similar pathway to Hartwig's cationic rhodium systems,[5d,e] and be distinctly different from the reaction mechanism proposed

for asymmetric HA reactions between norbornene and aniline using electron-rich, neutral iridium catalysts.[17] Our postulated mechanism is in line with several observations: 1) liberation of COD (or its hydrogenated derivatives) or hydride formation could not be observed at any point during these conversion runs; 2) catalyst **3**[X] is relatively insensitive to the electronic nature of the *N*-substituent;[18] 3) the overall electronic structure of **3**[X] (cationic complex, COD ligand) disfavors a classical N-H oxidative addition / insertion / reductive elimination pathway; 4) a mechanistically related reaction that relies on such an external attack of the amine (asymmetric ring-opening amination of oxabicycles),[19] can be performed successfully under absolutely identical reaction conditions (Scheme 2, middle).

For some of the more challenging reaction runs, NMR analysis of the mixture at the end of the catalytic run revealed that part of the catalyst had transformed back to the neutral, catalytically inactive (NHC)Ir(COD)Cl (**2**) precursor as evidenced by the appearance of diagnostic signals in ^{1}H NMR as well as ^{13}C NMR (see SI for details). Complex **2** in fact arises from the reaction of the pyrrolidine product with the methylene chloride solvent (Scheme 2, bottom). This type of nucleophilic substitution reaction (Menshutkin reaction) is generally very slow (half-life for trimethylamine and CH_2Cl_2 of a month),[20] but seems to be greatly facilitated by the presence of the cationic $[(NHC)Ir(COD)]^+$ species.[21] The resulting ammonium salt was identified via high resolution mass spectrometry.

The generation of neutral chloro complex **2** during catalysis unfortunately also leads to product contamination as it cannot be separated and removed efficiently during workup and column chromatographic purification of the product. After unsuccessfully applying a literature procedure used for removal of Grubbs-type ruthenium catalyst contaminants,[22] we developed a protocol where the cationic iridium complex is reformed and separated by extracting the product into a non-polar solvent at the beginning of the purification procedure (see SI for details).[23]

Two decades after Togni *et al.* had shown that neutral iridium catalysts effect the asymmetric hydroamination between norbornene and aniline,[24] we herein report a cationic iridium system that is able to cyclize unactivated aminoalkenes with unprecedented ease to give optically enriched pyrrolidine, piperidine and indoline products. The present system achieves this by using a chiral, monodentate NHC ligand and by incorporating the NTf_2 anion, yielding a catalyst that easily matches and exceeds results obtained with the latest reference zirconium systems and at the same time overcomes their lack of functional group tolerance. The catalyst platform disclosed here will serve as a basis for our continued efforts into expanding the utility of such chiral NHC ligands and pertinent developments will be discussed in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization of compounds (PDF).

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REFERENCES

(1) For selected reviews on the HA reaction: (a) Müller, T. E.; K. C. Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (b) Hannedouche, J.; Schulz, E. *Chem. Eur. J.* **2013**, *19*, 4972. (c) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem. Rev.* **2015**, *115*, 2596. (d) Bernoud, E.; Lepori, C.; Mellah, M.; Schulz, E.; Hannedouche, J. *Catal. Sci. Technol.* **2015**, *5*, 2017.

(2) (a) Gagné, M. R.; Brard, L.; Conticello, V.; Giardello, M. A.; Stern, C. L.; Marks, T. J. *Organometallics* **1992**, *11*, 2003. (b) Conticello, V. P.; Brard, L.; Giardello, M. A.; Tsuji, Y.; Sabat, M.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 2761. (c) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241.

(3) For catalytic systems providing >90 % ee for at least two pyrrolidine-type products; with rare-earth/group 4 metals, see: (a) Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748. (b) Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 354. (c) Manna, K.; Xu, S.; Sadow, A. D. *Angew. Chem. Int. Ed.* **2011**, *50*, 1865. (d) Manna, K.; Kruse, M. L.; Sadow, A. D. *ACS Catal.* **2011**, *1*, 1637. (e) Manna, K.; Everett, W. C.; Schoendorf, G.; Ellern, A.; Windus, T. L.; Sadow, A. D. *J. Am. Chem. Soc.* **2013**, *135*, 7235. (f) Manna, K.; Eedugurala, N.; Sadow, A. D. *J. Am. Chem. Soc.* **2015**, *137*, 425. (g) Zhou, X.; Wei, B.; Sun, X.-L.; Tang, Y.; Xie, Z. *Chem. Commun.* **2015**, *51*, 5751. With Mg, see: (h) Zhang, X.; Emge, T. J.; Hultzsch, K. C. *Angew. Chem. Int. Ed.* **2012**, *51*, 394.

(4) Other LTM systems need to use either electronically activated amines and/or activated olefins (see ref [1c]). Most noteworthy recent developments have introduced formal HA reactions using electron-poor amines and an additional exogenous hydrogen source that are mediated by chiral Cu catalysts. For first reports: (a) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 10830. (b) S. Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746. For a first example of an asymmetric intramolecular HA reaction with this system, see: (c) Wang, H.; Yang, J. C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 8428. For an overview: (d) Pirnot, M. T.; Wang, Y.-M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 48.

(5) (a) Shen, X.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 564. For reaction development and mechanistic insights of non-chiral cationic rhodium systems, see: (b) Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 6042. (c) Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570. (d) Julian, L. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 13813. (e) Liu, Z.; Yamamichi, H.; Madrahimov, S. T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2772.

(6) (a) Hesp, K. D.; Stradiotto, M. *Org. Lett.* **2009**, *11*, 1449. (b) Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 413.

(7) For examples that feature non-chiral NHCs within chelates: (a) Bauer, E. B.; Andavan, G. T. S.; Hollis, T. K.; Rubio, R. J.; Cho, J.; Kuchenbeiser, G. R.; Helgert, T. R.; Letko, C. S.; Tham, F. S. *Org. Lett.* **2008**, *10*, 1175. (b) Specht, Z. G.; Cortes-Llamas, S. A.; Tran, H. N.; Van Niekerk, C. J.; Rancudo, C. J.; Golen, J. A.; Moore, C. E.; Rheingold, A. L.; Dwyer, T. J.; Grotjahn, D. B. *Chem. Eur. J.* **2011**, *17*, 6606. (c) Zhang, R.; Xu, Q.; Mei, L. Y.; Li, S. K.; Shi, M. *Tetrahedron* **2012**, *68*, 3172. For an Au-catalyzed hydroamidation with IPr: (d) Li, H.; Widenhoefer, R. A. *Org. Lett.* **2009**, *11*, 2671.

(8) Sipos, G.; Ou, A.; Skelton, B. W.; Falivene, L.; Cavallo, L.; Dorta, R. *Chem. Eur. J.* **2016**, *22*, 6939.

(9) (a) Luan, X.; Mariz, R.; Robert, C.; Gatti, M.; Blumentritt, S.; Linden, A.; Dorta, R. *Org. Lett.* **2008**, *10*, 5569. (b) X. Luan, X.; L. Wu, L.; E. Drinkel, E.; R. Mariz, R.; M. Gatti, M.; R. Dorta, R. *Org. Lett.* **2010**, *12*, 1912. (c) Wu, L.; Falivene, L.; Drinkel, E.; Grant, S.; Linden, A.; Cavallo, L.; Dorta, R. *Angew. Chem. Int. Ed.* **2012**, *51*, 2870.

(10) The ligand has recently been synthesized by Ogoshi: Kumar, R.; Tamai, E.; Ohnoshi, A.; Nishimura, A.; Hoshimoto, Y.; Ohashi, M.; Ogoshi, S. *Synthesis* **2016**, *48*, 2789.

(11) Cationic iridium species are known to be sensitive to such changes, with [$BArF_{24}$] providing superior catalysts, *e.g.* see: Woodmansee, D. H.; Pfaltz, A. In *Iridium Catalysis*; Anderson, P. G., Ed.; Springer-Verlag, Berlin/Heidelberg, 2011; Chapter 3, pp 31-76.

(12) For reports on the synthesis of such iridium complexes: (a) Hintermair, U.; Gutel, T.; Slawin, A. M. Z.; Cole-Hamilton, D. J.; Santini, C. C.; Chauvin, Y. *J. Organomet. Chem.* **2008**, *693*, 2407. (b) Hintermair, U.; Englert, U.; Leitner, W. *Organometallics* **2011**, *30*, 3726. (c) Bohle, D. S.; Chua, Z. *Organometallics* **2015**, *34*, 1074.

(13) The [NTf_2] anion is by now well established in group 11 chemistry/catalysis: (a) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028. (b) Zheng, Z.; Wang, Z.; Wang, Y.; Zhang, L. *Chem. Soc. Rev.* **2016**, *45*, 4448. (c) Zi, W.; Toste, F. D. *Chem. Soc. Rev.* **2016**, *45*,4567.

(14) For an analysis of steric parameters, see: Sigman, M. S.; Miller, J. J. *J. Org. Chem.* **2009**, *74*, 7633.

(15) For an overview, see: (a) Kirk, K. L. In *Fluorinated Heterocyclic Compounds; Synthesis, Chemistry and Applications*; Petrov, V. A., Ed.; Wiley & Sons, New Jersey, 2009; Chapter 2, pp 91-158. For recent synthetic efforts: (b) Si, C.; Fales, K. R.; Torrado, A.; Frimpong, K.; Kaoudi, T.; Vandeveer, H. G.; Njoroge, F. G. *J. Org. Chem.* **2016**, *81*, 4359. (c) Fedorov, O. V.; Struchkova, M. I.; Dilman, A. D. *J. Org. Chem.* **2017**, *82*, 3270.

(16) **3**[X] does not need to be part of the catalytic cycle and substitution of the product by the new incoming aminoolefin might be associative.

(17) Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220, and references cited therein.

(18) A pathway going through initial oxidative addition of the amine would very likely show significant differences in rates depending on subtle electronic changes of the amine, see: Sykes, A. C.; White, P.; Brookhart, M. *Organometallics* **2006**, *25*, 1664.

(19) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 14884.

(20) (a) Menshutkin, N. *Z. Phys. Chem. Stoechiom. Verwandtschaftsl.* **1890**, *6*, 41. (b) Nevstad, G. O.; Songstad, J. *Acta Chem. Scand.* **1984**, *38*, 469.

(21) The most likely scenario would be that the cationic catalyst interacts with DCM, rendering its carbon atom more electrophilic and more susceptible to attack by the amine.

(22) Cho, J. H.; Kim, B. M. *Org. Lett.* **2003**, *5*, 531.

(23) The method developed here should be successful for neutral **GI** and **GII** catalysts, where contamination of the product is a major concern.

(24) Dorta, R.; Egli, P.; Zurcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857.

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