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2-Pyridonate Tantalum Complexes for the Intermolecular Hydroaminoalkylation of Sterically Demanding Alkenes

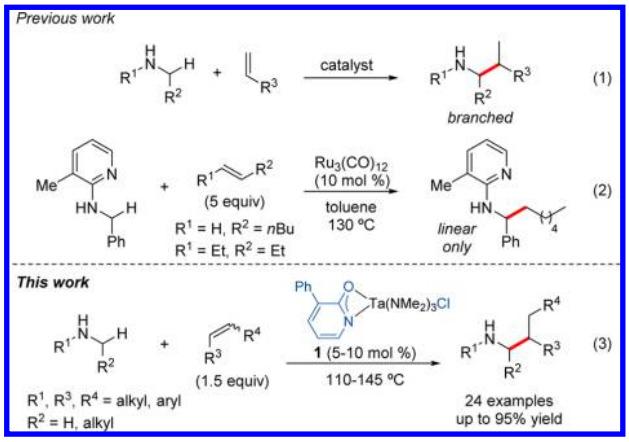
Eugene Chong, Jason W. Brandt, and Laurel L. Schafer*

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, British Columbia, Canada V6T 1Z1

Supporting Information

ABSTRACT: The design and synthesis of a mixed 2-pyridonate-Ta(NMe_2)$_3$Cl complex for the direct C−H alkylation adjacent to nitrogen in unprotected secondary amines are reported. The hydroaminoalkylation of sterically demanding internal alkenes gives the direct, catalytic formation of C(sp^3)−C(sp^3) bonds. Substrate scope investigations reveal key strategies for further catalyst development efforts in this 100% atom-economic synthesis of α-alkylated amines.

Catalytic alkene functionalization is an important avenue for the efficient synthesis of organic building blocks for synthesis.[1] In particular, the direct synthesis of selectively substituted amines by the catalytic functionalization of alkenes can be realized by hydroamination[2] and, more recently, hydroaminoalkylation.[3] The latter is the addition of an α-C(sp^3)−H bond adjacent to nitrogen across a C=C bond of unactivated alkenes (eq 1). This emerging early transition metal

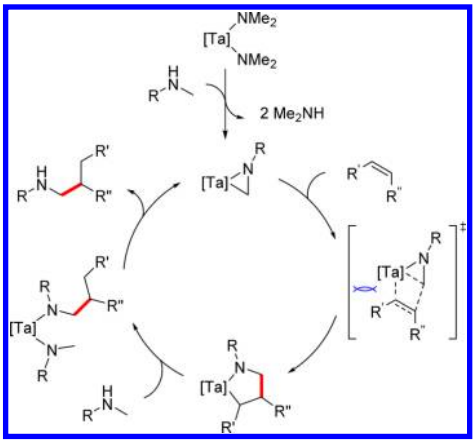


catalytic reaction is particularly attractive as it does not require additives, installation of protecting/directing groups, terminal oxidants, or photoinitiators. Thus, this catalytic C(sp^3)−C(sp^3) bond-forming reaction shows promise for the atom-economic synthesis of α-alkylated amines, which are important products for the fine chemical, pharmaceutical, and agrochemical industries. Here we report the first example of a hydroaminoalkylation precatalyst that can effect the direct α-alkylation of unprotected secondary amines with sterically demanding internal alkene substrates to give only the branched products.

Previous work using early transition metal (Ti, Zr, Ta, Nb) catalysts[4−6] has been largely limited to terminal alkene substrates to access methyl-branched products (eq 1).[7] This observed regioselectivity complements reported late transition metal (Ru and Ir) catalysts[8] that incorporate a pyridyl directing group to afford only linear products with *both* terminal *and* internal alkene substrates (eq 2).[8a,b] In these cases, internal alkenes undergo isomerization to terminal alkenes prior to hydroaminoalkylation and selective C−C bond formation at the terminal position.[8a,b] Previous to this report, there has been no catalytic hydroaminoalkylation system that can efficiently functionalize various sterically demanding and electronically challenging unactivated internal alkenes without C=C bond isomerization. Our group has shown that the simple organometallic reagent $TaMe_3Cl_2$ can afford the alkylated product in low yields with select *Z*-alkenes and, notably, no reactivity with *E*-alkenes was observed.[6n] Here we report the development of a sterically accessible and electrophilic tantalum precatalyst **1**, featuring a mixed 2-pyridonate/chloride ligand motif, that can realize the efficient catalytic hydroaminoalkylation of a variety of sterically demanding *E*- and *Z*-alkenes (eq 3) to give the anticipated branched products, with no isomerization of the alkene substrate.

A survey of reported hydroaminoalkylation catalysts shows that electrophilic and sterically demanding systems are critical for realizing effective reactivity with terminal alkenes.[6d−m] More specifically, enhanced reactivity has been observed with electron-withdrawing chloro and phosphoramidate ligands.[6d,m,n] However, internal alkenes could not be accommodated using such systems. Here we aimed to promote

Scheme 1. Proposed Mechanism for Hydroaminoalkylation



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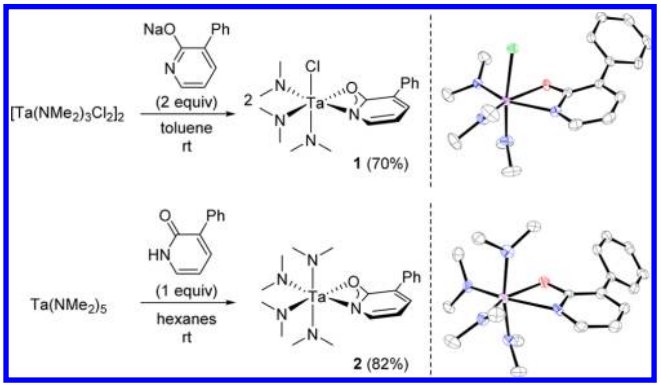
reactivity with more sterically demanding substrates, such as unactivated internal alkenes, by strategically preparing a system with reduced steric congestion about the metal center. As shown in Scheme 1, this design was anticipated to accommodate the insertion of bulky disubstituted alkenes (R′ and R″ ≠ H) into the reactive M−C bond of the key metallaziridine intermediates.[6b−e,j] Thus, the combination of electron-withdrawing 2-pyridonate[4i,5] and chloride ligands was selected to provide a sterically accessible, yet tunable metal center, with variable ligands, to access reactivity with internal alkene substrates (Scheme 2).

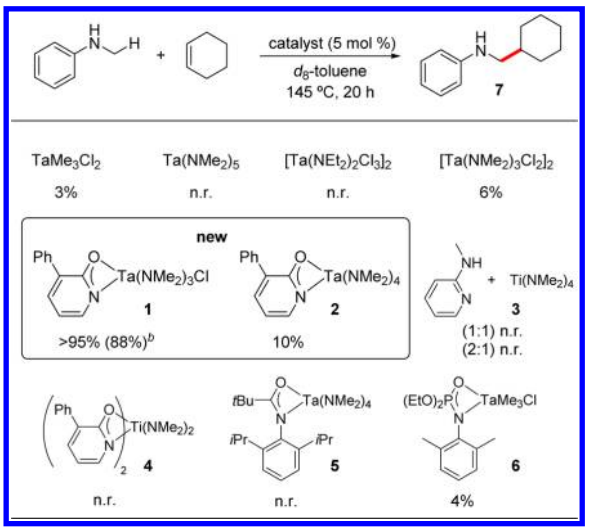
Scheme 2. Synthesis of 2-Pyridonate Tantalum Complexes



Few examples of 2-pyridonate-supported group 5 complexes have been reported,[9] and only one vanadium example has been explored for catalysis—specifically, polymerization catalysis.[9c] Here our targeted 2-pyridonate tantalum complexes **1** and **2** have been synthesized by salt metathesis and protonolysis reactions, respectively, and have been fully characterized (Scheme 2). Dimethylamido ligands have been selected to provide robustness, as previously reported alkyl complexes $TaMe_3Cl_2$[6n] and phoshoramidate-$TaMe_3Cl$[6m] are both heat- and light sensitive. The solid-state molecular structures of both **1** and **2** reveal a distorted trigonal bipyramidal geometry with asymmetric κ^2-*N*,*O*-binding of the 2-pyridonate on tantalum [**1**: Ta−O 2.130(2) Å, Ta−N 2.289(3) Å; **2**: Ta−O 2.150(7) Å, Ta−N 2.332(8) Å]. All of the dimethylamido N atoms in **1** and **2** exhibit multiple-bonding character to tantalum due to π-donation, as deduced from the trigonal planar sp^2-hybridization at the N atom and the short Ta−NMe_2 bond lengths [1.950(3)−2.057(9) Å].[10] The distinguishing structural feature of **1** is that the Ta−Cl bond [2.4959(8) Å] is significantly longer than Ta−$NMe_{2(axial)}$ bond [1.970(3) Å] and, generally, the bonding the of Ta−N amido bond lengths are shorter in **1** than in **2**.[10] These observations are consistent with improved metal accessibility and increased electrophilic nature of the metal center in **1** over **2**.

Catalyst screening began with targeting the known challenging hydroaminoalkylation of cyclohexene (Chart 1). Our group has previously reported the use of $TaMe_3Cl_2$ in the only early transition metal catalyzed example of this reaction.[6n] However, catalyst loadings of 10 mol% and extended reaction times (88 h) were required to achieve a modest yield of 47%. Here we use standardized reaction conditions of 5 mol% catalyst loading at 145 °C for comparative purposes. In this case, simple tantalum complexes, including $TaMe_3Cl_2$,[6n] $Ta(NMe_2)_5$,[6c] and $[Ta(NEt_2)_2Cl_3]_2$,[6d] all have minimal to no observed reactivity. Gratifyingly, 5 mol% of the sterically

Chart 1. Catalyst Screening[a]



[a]Reaction conditions: amine (0.5 mmol), cyclohexene (0.75 mmol), catalyst (0.025 mmol) d_8-toluene (0.5 mL). Conversion determined by ^{1}H NMR spectroscopy. n.r. = no reaction. [b]Isolated yield.

accessible complex **1**, with the mixed 2-pyridonate/chloride ligand motif, smoothly catalyzes the hydroaminoalkylation of cyclohexene within 20 h, with no discernible byproducts. However, when the small, electron-withdrawing chloride ligand is replaced by a more sterically demanding dimethylamido ligand, as in complex **2**, the reactivity of the precatalyst is dramatically reduced. Group 5 metals in particular are shown to be important, as titanium complexes with either amino-pyridinate **3**, as previously reported by Doye,[4g] or our disclosed titanium pyridonate complex **4**,[4i] are unreactive for this challenging transformation. However, group 5 catalysts must possess suitable steric and electronic features as our previously reported bulky *N*,*O*-chelated tantalum systems, **5**[6e,k] and **6**,[6m] are not useful for this reaction. In addition, Hultzsch has reported a promising and very sterically demanding binaphtholate niobium complex to be unreactive with cyclohexene as a substrate.[6j] To evaluate the role of the pyridonate ligand, a comparison of amidate **5** with the 2-pyridonate analogue of **2** shows that having the substituents tied back in an aromatic backbone (**2**), yields a slight improvement in reactivity (10% conv). Furthermore, the substitution of the 2-pyridonate ligand of **1** with another chloride, as in $[Ta(NMe_2)_3Cl_2]_2$, gives sluggish reactivity (6% conv). The key role of the pyridonate ligand is postulated to be due to its known hemi-lability, thereby affording variable steric congestion about the metal center throughout the catalytic reaction.

Encouraged by the excellent hydroaminoalkylation reactivity of **1** with cyclohexene, we further investigated a variety of sterically demanding disubstituted alkenes (Table 1). Ring sizes ranging from 5 to 12 carbons undergo hydroaminoalkylation in good to excellent yields (entries 1−5). Cycloheptene is the most reactive substrate with efficient reactivity being observed at 130 °C (entry 3), whereas the small cyclopentene (entry 1) and the *cis*/*trans*-mixture of cyclododecene (entry 5), require heating at 145 °C for up to 44 h. The hydroaminoalkylation of an unactivated diene is feasible to access monoalkylated product **8b** (entry 2), and a higher loading of 1,4-cyclohexadiene (3 equiv) helps to minimize the formation of dialkylated product. Linear alkenes are less reactive than the

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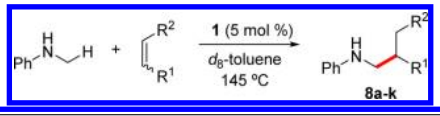
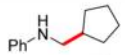
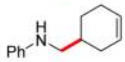
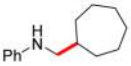
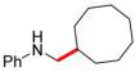
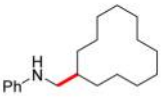
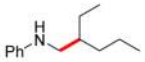
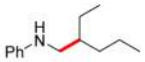
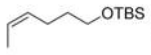
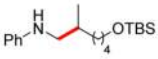
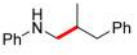
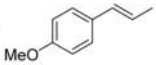
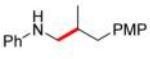
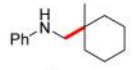
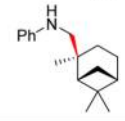
Table 1. Scope of Disubstituted Alkenes[a]



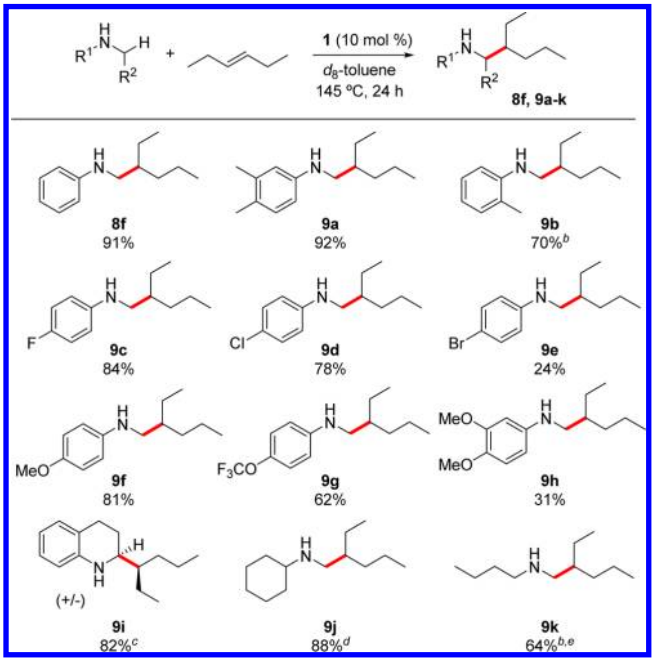
entry	alkene	product		cond.	yield (%)
1			8a	44 h	73
2[b]			8b	20 h	72
3			8c	130 °C 20 h	95
4			8d	20 h	93
5			8e	44 h	88
6			8f	44 h	79
7			8f	44 h	69
8			8g	44 h	70[c] (2.3:1)[d]
9			8h	24 h	92[c] (4.4:1)[d]
10[e]			8i	44 h	76[c] (2.0:1)[d]
11			8j	110 °C 20 h	91
12			8k	54 h	55 (15.9:1)[f]

[a]Reaction conditions: amine (0.5 mmol), alkene (0.75 mmol), **1** (0.025 mmol), d_8-toluene (0.5 mL). Isolated yield. [b]Diene (1.5 mmol). [c]Major isomer presented. Yields refer to combined regioisomers. [d]Ratio of regioisomers determined by GC analysis. [e]**1** (10 mol %). [f]Diastereomer ratio determined by GC analysis.

cyclic alkenes, with *E*-3-hexene (entry 6) being more reactive than the *Z*-3-hexene (entry 7). This is the first example of hydroaminoalkylation with a linear *E*-alkene without C=C bond migration.[8a,b,11] For unsymmetrical linear alkenes (entries 8–10), modest regioselectivities (up to 4.4:1) are seen with the preference for C–C bond formation at the sterically less-hindered carbon. An internal-*Z*-alkene with a silyl-protected alcohol is tolerated to access a protected amino alcohol derivative **8g** (entry 8). Previously, there had been no report of hydroaminoalkylation of *β*-substituted styrene derivatives. Gratifyingly, here *cis*-*β*-methylstyrene and *trans*-anethole undergo hydroaminoalkylation with modest regioselectivity (entries 9 and 10). For 1,1-disubstituted alkenes (entries 11 and 12), alkylation occurs at the more substituted carbon to generate a quaternary carbon center *β* to N in a single catalytic step. Methylenecyclohexane readily reacts at only 110 °C to give the hydroaminoalkylation product **8j** in 91% yield (entry 11). Notably, (1*S*)-*β*-pinene is alkylated with excellent diastereoselectivity (15.9:1, entry 12), providing the first example of hydroaminoalkylation of a naturally occurring terpene, and demonstrating tolerance of increased structural complexity.

With these examples of hydroaminoalkylation in hand, we then explored the amine substrate scope with *E*-3-hexene, a particularly challenging substrate (Chart 2). By utilizing an increased catalyst loading of 10 mol% of **1**, the hydroaminoalkylation product **8f** can be synthesized in excellent yield (91%) in shorter reaction times of 24 h. Substituents at the *para*- and *meta*-positions (**9a**) are tolerated on *N*-methylaniline derivatives. Substituents can even be tolerated at the *ortho*-position of *N*-methylaniline derivatives (**9b**), although longer reaction times are required. Halogen substituents including fluorine (**9c**) and chlorine (**9d**) are compatible for the reaction, while bromine (**9e**) is tolerated with less efficiency, resulting in modest product yields.[12] Interestingly, the presence of an electron-donating methoxy group (**9f**) does not compromise reactivity. Here we also show that the pharmaceutically relevant trifluoromethoxy group (**9g**) can be accommodated. However, the usage of the chelating catechol derivative (**9h**) impedes the reaction, and lower yields are observed.[12] Most importantly, this catalyst system is not limited to *N*-methylarylamines.[13] For example, tetrahydroquinoline can be used in hydroaminoalkylation to give a single diastereomeric product **9i**.[10] Furthermore, the known challenging dialkylamine substrates[6d] (**9j** and **9k**) can be used to give the regioselective product resulting from exclusive alkylation at the sterically less-hindered and kinetically preferred *N*-methyl carbon.

Chart 2. Scope of Amines[a]



[a]Reaction conditions: amine (0.5 mmol), alkene (0.75 mmol), **1** (0.05 mmol), d_8-toluene (0.5 mL). Isolated yield. [b]92 h. [c]Single diastereomer obtained. [d]44 h. [e]165 °C.

To date, terminal alkenes have been used for hydroaminoalkylation, and group 5 metal complexes have been largely limited to the synthesis of methylated products (**10**, Scheme 3). When we tested the more sterically accessible **1** with the standard terminal alkene substrate, 1-octene, the reaction does not reach full conversion, even with prolonged reaction times.

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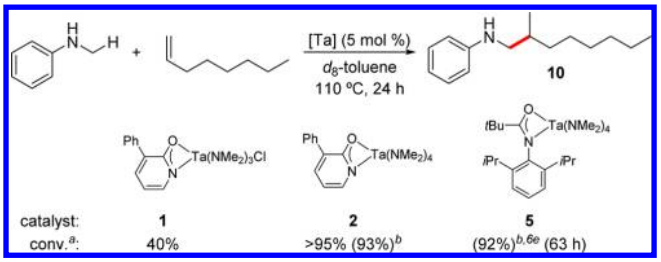
Scheme 3. Modifying Catalyst Design To Target Terminal Alkenes



[a]Reaction conditions same as Table 1. [b]Isolated yield.

However, the easily prepared and more sterically congested complex **2**, realizes full conversion to product **10** at only 110 °C in 24 h. This result compares favorably with our known amidate complex **5**.[6e] These reactivity trends suggest that steric bulk/congestion about the reactive metal center is required for hydroaminoalkylation catalytic turnover. When working with sterically less demanding terminal alkenes, more sterically demanding ligand sets are required for efficient catalytic turnover, while the more sterically accessible reactive complex **1** requires bulky substrates for good reactivity. Most importantly, these results show how the easily varied ligand environment of Ta can be used to advantage to prepare related complexes to address complementary classes of substrates.

In summary, we have developed the first precatalyst for the catalytic hydroaminoalkylation of unactivated, sterically demanding *E*- and *Z*-internal alkenes. Here we show that the combination of sterically less demanding and electron-withdrawing 2-pyridonate and chloride ligands on tantalum are preferred for accommodating such bulky substrates. Complex **1** also exhibits good amine substrate scope and excellent diastereoselectivities. Most importantly, these investigations illustrate how the easily varied ligand environment of Ta can be used to advantage in the design of mixed ligated complexes to access improved substrate scope. On-going work focuses on organometallic mechanistic investigations and catalyst development efforts toward enantioselective and regioselective transformations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization (^{1}H and ^{13}C NMR spectra), and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

schafer@chem.ubc.ca

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368.
(2) For a review of hydroamination, see: Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795 and references therein.
(3) For a review of hydroaminoalkylation, see: Roesky, P. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 4892.
(4) For Ti catalysts, see: (a) Müller, C.; Saak, W.; Doye, S. *Eur. J. Org. Chem.* **2008**, 2731. (b) Kubiak, R.; Prochnow, I.; Doye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 1153. (c) Prochnow, I.; Kubiak, R.; Frey, O. N.; Beckhaus, R.; Doye, S. *ChemCatChem* **2009**, *1*, 162. (d) Kubiak, R.; Prochnow, I.; Doye, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 2626. (e) Prochnow, I.; Zark, P.; Müller, T.; Doye, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 6401. (f) Jaspers, D.; Saak, W.; Doye, S. *Synlett* **2012**, *23*, 2098. (g) Dörfler, J.; Doye, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 1806. (h) Preuß, T.; Saak, W.; Doye, S. *Chem.—Eur. J.* **2013**, *19*, 3833. (i) Chong, E.; Schafer, L. L. *Org. Lett.* **2013**, *15*, 6002.
(5) For Zr catalyst, see: Bexrud, J. A.; Eisenberger, P.; Leitch, D. C.; Payne, P. R.; Schafer, L. L. *J. Am. Chem. Soc.* **2009**, *131*, 2116.
(6) For group 5 metal catalysts, see: (a) Clerici, M. G.; Maspero, F. *Synthesis* **1980**, 305. (b) Nugent, W. A.; Ovenall, D. W.; Holmes, S. J. *Organometallics* **1983**, *2*, 161. (c) Herzon, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 6690. (d) Herzon, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 14940. (e) Eisenberger, P.; Ayinla, R. O.; Lauzon, J. M. P.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 8361. (f) Eisenberger, P.; Schafer, L. L. *Pure Appl. Chem.* **2010**, *82*, 1503. (g) Zi, G.; Zhang, F.; Song, H. *Chem. Commun.* **2010**, *46*, 6296. (h) Zhang, F.; Song, H.; Zi, G. *Dalton Trans.* **2011**, *40*, 1547. (i) Reznichenko, A. L.; Emge, T. J.; Audörsch, S.; Klauber, E. G.; Hultzsch, K. C.; Schmidt, B. *Organometallics* **2011**, *30*, 921. (j) Reznichenko, A. L.; Hultzsch, K. C. *J. Am. Chem. Soc.* **2012**, *134*, 3300. (k) Payne, P. R.; Garcia, P.; Eisenberger, P.; Yim, J. C.-H.; Schafer, L. L. *Org. Lett.* **2013**, *15*, 2182. (l) Garcia, P.; Payne, P. R.; Chong, E.; Webster, R. L.; Barron, B. J.; Behrle, A. C.; Schmidt, J. A. R.; Schafer, L. L. *Tetrahedron* **2013**, *69*, 5737. (m) Garcia, P.; Lau, Y. Y.; Perry, M. R.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 9144. (n) Zhang, Z.; Hamel, J.-D.; Schafer, L. L. *Chem.—Eur. J.* **2013**, *19*, 8751. (o) Dörfler, J.; Doye, S. *Eur. J. Org. Chem.* **2014**, 2790.
(7) Strained norbornene is the only internal alkene that has been commonly reported to date.
(8) For Ru and Ir catalysts, see: (a) Jun, C.-H.; Hwang, D.-C.; Na, S.-J. *Chem. Commun.* **1998**, 1405. (b) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935. (c) Pan, S.; Endo, K.; Shibata, T. *Org. Lett.* **2011**, *13*, 4692. (d) Pan, S.; Matsuo, Y.; Endo, K.; Shibata, T. *Tetrahedron* **2012**, *68*, 9009. (e) Bergman, S. D.; Storr, T. E.; Prokopcová, H.; Aelvoet, K.; Diels, G.; Meerpoel, L.; Maes, B. U. W. *Chem.—Eur. J.* **2012**, *18*, 10393. (f) Schmitt, D. C.; Lee, J.; Dechert-Schmitt, A.-M. R.; Yamaguchi, E.; Krische, M. J. *Chem. Commun.* **2013**, *49*, 6096. (g) Schinkel, M.; Wang, L.; Bielefeld, K.; Ackermann, L. *Org. Lett.* **2014**, *16*, 1876.
(9) (a) Atiñolo, A.; Carrillo-Hermosilla, F.; Fernández-Baeza, J.; Fernández de Toro, A. M.; García-Yuste, S.; Otero, A.; Pérez-Flores, J. C.; Rodríguez, A. M. *Inorg. Chim. Acta* **2000**, *300*, 131. (b) Fandos, R.; Hernández, C.; Otero, A.; Rodríguez, A.; Ruiz, M. J.; Terreros, P. *Eur. J. Inorg. Chem.* **2003**, 493. (c) Nagy, S.; Cribbs, L. V.; Etherton, B. P.; Cocoman, M.; Krishnamurti, R.; Tyrell, J. A. U.S. Patent 6,759,493 B1, July 6, 2004.
(10) See Supporting Information.
(11) In the reaction of **1** and an excess of *E*-3-hexene (no amine substrate), dialkylation of dimethylamido ligands was observed,[6n] but no C=C bond isomerization was observed with the remaining *E*-3-hexene.
(12) Longer reaction times do not significantly improve the yield.
(13) Attempts to react other *N*-heterocycles, such as pyrrolidine, piperidine, and *N*-substituted piperazines, with *E*-3-hexene have been unsuccessful.