

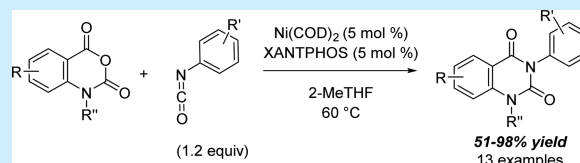
Nickel-Catalyzed Synthesis of Quinazolinones

Gregory L. Beutner,^{*†} Yi Hsiao, Thomas Razler, Eric M. Simmons, and William Wertjes

Chemical and Synthetic Development, Bristol-Myers Squibb Company, One Squibb Drive, New Brunswick, New Jersey 08903-0191, United States

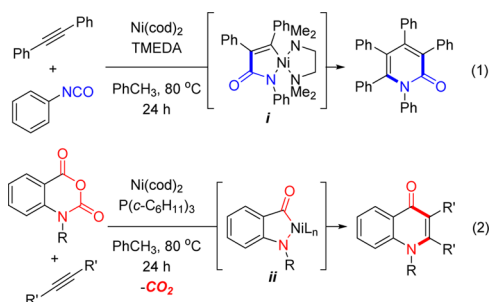
Supporting Information

ABSTRACT: A nickel(0)-catalyzed method for the synthesis of quinazolinones from isatoic anhydrides and isocyanates is described. High-throughput ligand screening revealed that XANTPHOS was the optimal ligand for this transformation. Subsequent optimization studies, supported by kinetic analysis, significantly expanded the reaction scope. The reaction exhibits a case of substrate inhibition kinetics with respect to the isocyanate. Preliminary results on an asymmetric synthesis of atropisomeric quinazolinones are reported.



Nickel(0)-catalyzed cycloadditions of unsaturated organic compounds comprise a large family of reactions that give access to unsaturated five- and six-membered rings.¹ When one of the components is an isocyanate, these transformations allow access to a broad range of heterocycles including pyridones,² pyrimidones,^{2a,3} amides,⁴ imides,⁵ and hydantoins.⁶ The reactions proceed via interaction of a nickel(0) complex with two π -bonds, leading to the formation of an aza-nickelacycle, as exemplified by intermediate *i* in the synthesis of pyridones from alkyne and isocyanate coupling partners (Scheme 1, eq 1).⁷

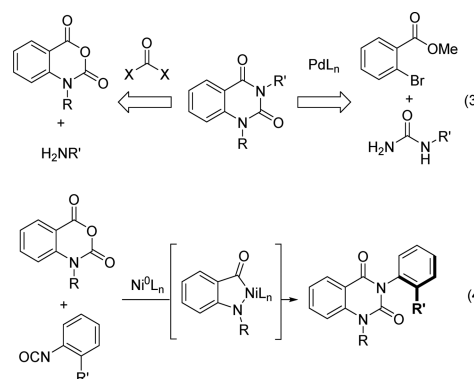
Scheme 1. Nickel(0)-Catalyzed Reactions with Isocyanates



Recently, it has been demonstrated that a similar nickelacycle *ii* can be accessed through decarboxylative insertion of a nickel(0) complex into an isatoic anhydride (eq 2),⁸ which can subsequently react with alkynes or alkenes to form quinoline and indole products depending on the reaction conditions.

As part of an ongoing drug discovery program, we became interested in the synthesis of *N*-arylquinazolinones.⁹ Several methods exist for the preparation of these heterocycles following a simple disconnection that leads back to an *o*-amino benzoic acid derivative, generally an isatoic anhydride (Scheme 2, eq 3).¹⁰ Ring opening with an amine, followed by cyclization with a carbonylating agent (e.g., carbonyldiimidazole, phosgene), leads to formation of the quinazolinone in good yields. The simplicity of this reaction and the ready availability of a wide range

Scheme 2. Synthetic Routes to Quinazolinones



of isatoic anhydrides makes it an excellent choice for preparation of these compounds. However, in the case of the desired *N*-arylquinazolinones where a potential chiral axis exists between N3 and the pendant aryl ring, such methods provide little opportunity for asymmetric induction. The synthesis of quinazolinones in the presence of copper or palladium catalysts starting from *o*-bromobenzoates may provide options through introduction of a chiral ligand, but these methods have not been demonstrated for the synthesis of the *N*-arylquinazolinones of interest.¹¹

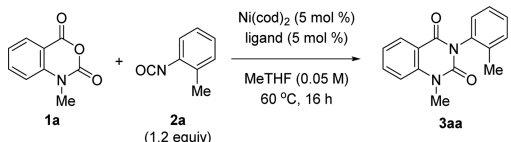
Recognizing the broad utility of isatoic anhydrides as an entry point to the synthesis of quinazolinones, we hypothesized that a nickel-catalyzed process could be developed to prepare these heterocycles from isatoic anhydrides and isocyanates (Scheme 2, eq 4). The asymmetric synthesis of 2-pyridones from aryl isocyanates has been achieved using rhodium or iridium catalysis,¹² but no similar atropisomer selective reactions are known for nickel. In addition, although isocyanates have been used in a number of nickel(0)-catalyzed processes, reactivity with

Received: January 6, 2017

isatoic anhydrides has not been demonstrated. In this report, we describe the development of a nickel(0)-catalyzed synthesis of quinazolinones from isocyanates and isatoic anhydrides.

Initial screening of the test reaction between *N*-methylisatoic anhydride (**1a**) and *o*-tolyl isocyanate (**2a**) using nickel(0) bis-cyclooctadiene (Ni(cod)₂) was conducted in 96-well plate format to rapidly assay a diverse set of ligands (Table 1).¹³ Monodentate

Table 1. Results of Achiral Ligand Screening



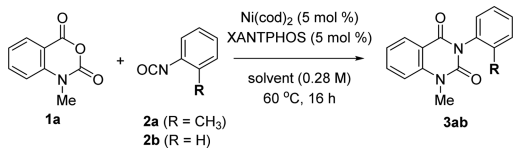
entry	ligand	conv ^a (%)	bite angle ¹⁶ (deg)
1	PPh ₃	41	NA
2	PCy ₃	18	NA
3	IPr	39	NA
4	SIPr	43	NA
5	XANTPHOS (4)	92	102
6	DPEPhos	48	105
7	DPPE	25	83
8	DPPP	40	92
9	DPPB	36	97
11	DPPF	40	99
11	BISBI	32	120
12	DBFphos	48	134
13	PHOX	79	NA

^aConversions are calculated on the basis of HPLC area % of **1a** and **2a**, adjusted for UV response factors.

ligands typically used in this class of transformations gave poor conversion (entries 1–4). Bidentate ligands gave better results, with XANTPHOS being the optimal ligand in terms of reaction conversion (entry 5).¹⁴ Examination of the closely related DPEPhos showed poor results, suggesting that the rigid conformation of XANTPHOS was critical toward attaining high reactivity (entry 6). A survey of bidentate ligands with a broad range of bite angles did not reveal any distinct trend (entries 7–12), consistent with the hypothesis that rigidity, rather than bite angle, is responsible for the high performance of XANTPHOS in this transformation. The only ligand that gave comparable reactivity to XANTPHOS was the phosphino-oxazoline ligand PHOX (entry 13). The success of the PHOX ligand was encouraging since a wide variety of chiral phosphino-oxazolines are available, while chiral analogues of XANTPHOS are not readily available.¹⁵ Additional solvent screening using XANTPHOS at a preparative scale revealed that noncoordinating solvents such as toluene gave high conversions, while more polar solvents such as *N,N*-dimethylacetamide showed lower levels of reactivity. Additionally, a 1:1 XANTPHOS/Ni ratio was found to be optimal, with excess ligand leading to significantly lower reaction rates.

Having identified the optimal reaction conditions, we moved to evaluate the reaction scope at a gram scale. Initial results for the reaction between **1a** and **2a** were excellent, but examination of additional substrates immediately revealed some limitations (Table 2, entries 1, 2). Surprisingly, the reaction of phenyl isocyanate (**2b**) showed a dramatic loss in reactivity. At this point, we suspected that the initial choice of substrates for ligand screening might have led to a ligand with poor generality; therefore, the original ligand set was re-examined using phenyl

Table 2. Effect of Isocyanate Stoichiometry



entry	isocyanate (equiv)	conv ^a (3 h, %)	conv ^a (20 h, %)	yield (%)
1	2a (1.2)	98	>99	98
2	2b (1.2)	10	22	ND
3	2b (2.4)	4	13	ND
4	2b (0.6)	48	54	ND
5	2b (1.2) ^b	54	67	ND
6	2b (1.2) ^c	93	97	83

^aConversions are calculated on the basis of HPLC area % of **1a** and **2a,b**, adjusted for UV response factors. ^bAddition of **2b** completed in two portions of 0.60 equiv. ^cSlow addition of **2b** over 1 h.

isocyanate **2b**. To our surprise, XANTPHOS was again identified as the optimal ligand with few other ligands showing sufficiently high reactivity to warrant further investigation. Since the Ni(0)–XANTPHOS catalyst showed different performance at a screening scale when compared to the gram scale for the reaction of **1a** and **2b**, we sought to understand this difference and, thus, extend the reactivity of our initial screening hit. However, examination of overall reaction concentration, addition order, temperature, presence of cyclooctadiene (COD), and headspace volume showed that none of these factors had a significant influence on the efficiency of the Ni–XANTPHOS-catalyzed process at larger scales.

It was not until we began to investigate the stoichiometry of the process that a path forward was identified. Based on concerns about the stability of the isocyanate,¹⁷ the loading of the isocyanate was varied. Although larger amounts of isocyanate did not lead to improved conversions, lower amounts did (entries 2–4). On the basis of this result, portionwise addition was explored, which led to a further increase in conversion. Finally, slow addition of isocyanate **2b** over 1 h led to very high conversions, comparable to what had originally been observed at the screening scale (entry 6). This result suggested that having excess isocyanate relative to catalyst may lead to catalyst inhibition, possibly due to formation of an inactive, off-cycle intermediate bound to excess isocyanate. Although it was unclear at this stage why this change allowed us to translate the screening scale results to preparative scale, we elected to use this slow-addition method to continue exploring the reaction scope.

As shown in Figure 1, the slow addition protocol greatly broadened the reaction scope but was not required in all cases. Curiously, it appeared that the more sterically hindered isocyanates were more reactive. The slow addition protocol allowed for the synthesis of quinazolinones devoid of *ortho*-substituents on the aryl ring as well as alkyl isocyanates, opening access to a small family of natural products.^{10a,18} In contrast to the broad scope of isocyanates that could be employed, the isatoic anhydride component showed more significant limitations that could not be overcome by the slow addition protocol or reoptimization of the ligand. Although substitution on the distal aryl ring was tolerated, changes to the N1-substituent were not. In the case of the parent isatoic anhydride (R' = H) and the *N*-benzyl isatoic anhydride, no reaction was observed, even using slow addition or higher temperatures in toluene. Some reactivity was observed in the case of the *N*-phenyl- and *N*-isopropylisatoic

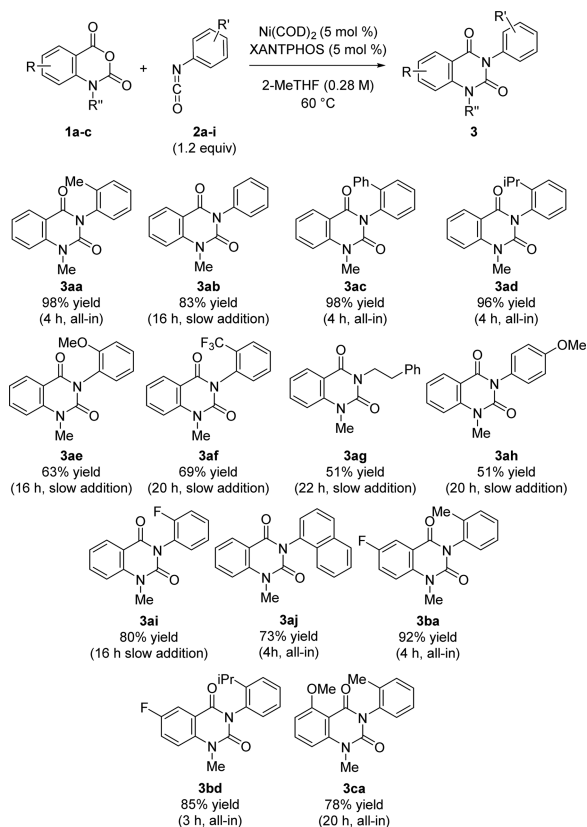


Figure 1. Reaction scope with the Ni(0)-XANTPHOS catalyst system.

anhydrides, but even at 100 °C in toluene, conversions could not be driven beyond 50% after 16 h.

Although a solution to the initial limitations on the substrate scope had been found, we remained curious about the sluggish reactivity of the less hindered isocyanates like phenyl isocyanate 2b. We sought to gain additional information about the reaction through a combination of spectroscopic and kinetic studies. ³¹P NMR studies were not revealing since the catalyst resting state appeared to be Ni(XANTPHOS)₂ (5). Several transient species were observed, but only at low levels, and they could not be identified. Kinetic studies of the reaction of 1a and 2a based on HPLC analysis of reaction aliquots provided more information.¹³ A curious rate dependence was observed with respect to the isocyanate 2a (Figure 2). Two kinetic regimes are clear: one at low concentrations of 2a where the rate is increasing with the concentration of isocyanate and a second at higher concentrations of 2a where the rate is decreasing with the concentration

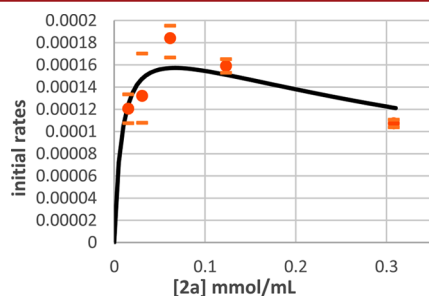
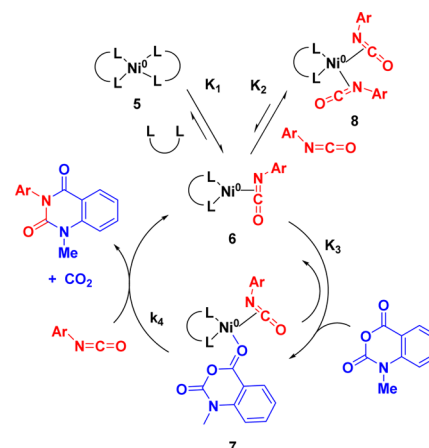


Figure 2. Dependence of initial rate on concentration of 2a and fitting to a substrate inhibition model ($d[3aa]/dt = k_4K_1K_3[Ni]_0[1a][2a]/(1 + K_1([2a]/[4]) + K_1K_3[1a][2a] + K_1K_2[2a]^2)$) shown in Scheme 3.

of isocyanate. The data fit nicely to a substrate inhibition model¹⁹ where binding of one molecule of isocyanate to nickel would lead to an active catalyst and binding of the second isocyanate would lead to an inactive complex, competing with productive binding of the isatoic anhydride.

We propose the mechanism depicted in Scheme 3 to account for these observations. Ni(XANTPHOS)₂ (5)^{14,20} undergoes a

Scheme 3. Proposed Mechanism for Catalyst Activation

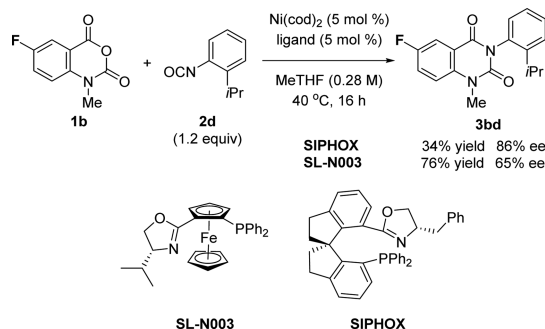


dissociative ligand exchange with isocyanate to generate the active intermediate 6. This proposal is consistent with the negative impact of excess XANTPHOS on reaction rate. Productive binding of the isatoic anhydride to 6 would generate 7, which could then proceed on to the rate-determining carbon-oxygen bond-insertion step.²¹ If binding of an additional isocyanate to 6 competes with the isatoic anhydride it would lead to an inactive, off-cycle intermediate 8. The scenario sets up a competition between active complex 6 and inactive complex 8. In the complex 6, the presence of an *ortho*-substituent may disfavor η^2 -binding of a second isocyanate in favor of a more compact, single-point binding to the isatoic anhydride.²² The general form of this mechanism shows a number of similarities with the proposed mechanism of nickel(0)-catalyzed cycloadditions between alkynes and isatoic anhydrides, including the hypothesis that it is an alkyne-bound nickel(0) catalyst which is the active catalyst intermediate.²³

Having gained some knowledge of the scope and type of ligand required for the transformation to proceed, the asymmetric version of the process was investigated. A chiral ligand screen was undertaken, favoring P,N ligands such as phosphino-oxazoline ligands,²⁴ but representatives from other chiral ligand classes were also examined. Reactions were run at 40 °C using 1b and 2d to minimize the chance of racemization in the product 3bd through rotation of the carbon-nitrogen chiral axis. As expected, chiral P,N ligands such as SL-N003 and SIPHOX gave moderate to good levels of selectivity (Scheme 4).¹³ This is consistent with the observations of Murakami and co-workers who found PHOX ligands optimal in a related nickel(0) catalyzed transformation.^{3b}

In summary, we have developed a nickel(0)-catalyzed synthesis of quinazolinones from readily available isatoic anhydrides and isocyanates. Leveraging the power of ligand screening, both achiral and chiral ligands were found that promotes this transformation. Despite encountering some initial limitations in terms of scope, high yields could be obtained with a broad range of substrates by employing a slow addition protocol. The rationale behind the need for slow addition of the isocyanate

Scheme 4. Asymmetric Synthesis of Quinazolinodione 3bd



is explained through substrate inhibition of the nickel(0) catalyst by unproductive binding of a second molecule of isocyanate to a key catalyst intermediate. It is anticipated that the clues provided in these studies about the key factors affecting this fruitful class of reactions can aid in its extension to even more complex and challenging substrates.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00052.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gregory.beutner@bms.com.

ORCID

Gregory L. Beutner: 0000-0001-8779-1404

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Mr. Sloan Ayers (BMS) for assistance with MS and NMR analysis, Dr. Matthew Winston (BMS) for helpful discussions, and Dr. Robert Waltermire (BMS) for supporting this work.

■ REFERENCES

- (1) (a) Thakur, A.; Louie, J. *Acc. Chem. Res.* **2015**, 48, 2354. (b) Kumar, P.; Louie, J. In *Transition-Metal-Mediated Aromatic Ring Construction*; Tanaka, K., Ed.; Wiley: New York, 2013; Chapter 2, p 37. (c) Saito, S. In *Modern Organonickel Chemistry*; Tamaru, Y., Ed.; Wiley-VCH: Weinheim, 2005; Chapter 6, p 171.
- (2) (a) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1983**, 252, 359. (b) Duong, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc.* **2004**, 126, 11438. (c) Duong, H. A.; Louie, J. *J. Organomet. Chem.* **2005**, 690, 5098. (d) Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, 49, 4786. (e) Hoberg, H.; Oster, B. W. *Synthesis* **1982**, 1982, 324.
- (3) (a) Morimoto, M.; Nishida, Y.; Miura, T.; Murakami, M. *Chem. Lett.* **2013**, 42, 550. (b) Miura, T.; Morimoto, M.; Murakami, M. *J. Am. Chem. Soc.* **2010**, 132, 15836. (c) Duong, H. A.; Louie, J. *Tetrahedron* **2006**, 62, 7552.
- (4) (a) D'Souza, B. R.; Louie, J. *Org. Lett.* **2009**, 11, 4168. (b) Schleicher, K. D.; Jamison, T. F. *Org. Lett.* **2007**, 9, 875. (c) Hoberg, H.; Bärhausen, D.; Mynott, R.; Schroth, G. *J. Organomet. Chem.* **1991**, 410, 117. (d) Hoberg, H.; Bärhausen, D. *J. Organomet. Chem.* **1990**, 397, C20.

- (e) Hoberg, H.; Nohlen, M. *J. Organomet. Chem.* **1990**, 382, C6.
- (f) Hernandez, E.; Hoberg, H. *J. Organomet. Chem.* **1987**, 327, 429.
- (5) (a) Hoberg, H.; Nohlen, M. *J. Organomet. Chem.* **1991**, 412, 225. (b) Hoberg, H.; Sümmerrmann, K.; Hernandez, E.; Rupp, C.; Guhl, D. *J. Organomet. Chem.* **1988**, 344, C35. (c) Hernandez, E.; Hoberg, H. *J. Organomet. Chem.* **1986**, 315, 245. (d) Hoberg, H.; Sümmerrmann, K.; Milchereit, A. *J. Organomet. Chem.* **1985**, 288, 237. (e) Hoberg, H.; Sümmerrmann, K. *J. Organomet. Chem.* **1984**, 275, 239.
- (6) Miura, T.; Mikano, Y.; Murakami, M. *Org. Lett.* **2011**, 13, 3560.
- (7) (a) Ohashi, M.; Hoshimoto, Y.; Ogoshi, S. *Dalton Trans.* **2015**, 44, 12060. (b) Eisch, J. J.; Aradi, A. A.; Lucarelli, M. A.; Qian, Y. *Tetrahedron* **1998**, 54, 1169. (c) Hoberg, H.; Guhl, D.; Betz, P. *J. Organomet. Chem.* **1990**, 387, 233. (d) Eisch, J. J.; Galle, J. E.; Aradi, A. A.; Boleslawski, M. P. *J. Organomet. Chem.* **1986**, 312, 399. (e) Hoberg, H.; Sümmerrmann, K. *J. Organomet. Chem.* **1983**, 253, 383. (f) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1982**, 234, C35. (g) Eisch, J. J.; Galle, J. E. *J. Organomet. Chem.* **1975**, 96, C23.
- (8) (a) Sun, M.; Ma, Y.-N.; Li, Y.-M.; Tian, Q.-P.; Yang, S.-D. *Tetrahedron Lett.* **2013**, 54, 5091. (b) Nakai, K.; Kurahashi, T.; Matsubara, S. *Chem. Lett.* **2013**, 42, 1238–1240. (c) Yoshino, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2009**, 131, 7494.
- (9) Watterson, S. H.; De Lucca, G. V.; Shi, Q.; Langevine, C. M.; Liu, Q.; Batt, D. G.; Bertrand, M. B.; Gong, H.; Dai, J.; Yip, S.; Li, P.; Sun, D.; Wu, D.-R.; Wang, C.; Zhang, Y.; Traeger, S. C.; Pattoli, M. A.; Skala, S.; Cheng, L.; Obermeier, M. T.; Vickery, R.; Discenza, L. N.; D'Arienzo, C. J.; Zhang, Y.; Heimrich, E.; Gillooly, K. M.; Taylor, T. L.; Pulicicchio, C.; McIntyre, K. W.; Galella, M. A.; Tebben, A. J.; Muckelbauer, J. K.; Chang, C.; Rampulla, R.; Mathur, A.; Salter-Cid, L.; Barrish, J. C.; Carter, P. H.; Fura, A.; Burke, J. R.; Tino, J. A. *J. Med. Chem.* **2016**, 59, 9173.
- (10) (a) Li, X.; Lee, Y. R. *Bull. Korean Chem. Soc.* **2011**, 32, 2121. (b) Tran, T. P.; Ellsworth, E. L.; Watson, B. M.; Sanchez, J. P.; Showalter, H. D. H.; Rubin, J. R.; Stier, M. A.; Yip, J.; Hguyen, D. Q.; Bird, P.; Singh, R. *J. Heterocycl. Chem.* **2005**, 42, 669. (c) Rivero, I. A.; Espinoza, K.; Somanathan, R. *Molecules* **2004**, 9, 609.
- (11) (a) Guy, C. S.; Jones, T. C. *Synlett* **2009**, 2009, 2253. (b) Willis, M. C.; Snell, R. H.; Fletcher, A. J.; Woodward, R. L. *Org. Lett.* **2006**, 8, 5089.
- (12) (a) Onodera, G.; Suto, M.; Takeuchi, R. *J. Org. Chem.* **2012**, 77, 908. (b) Tanaka, K.; Takahashi, Y.; Suda, T.; Hirano, M. *Synlett* **2008**, 2008, 1724. (c) Tanaka, K.; Wada, A.; Noguchi, K. *Org. Lett.* **2005**, 7, 4737.
- (13) See the Supporting Information for a description and results.
- (14) The unique reactivity of XANTPHOS in Ni(0) systems has been observed previously: (a) Staudaheer, N. D.; Stolley, R. M.; Louie, J. *Chem. Commun.* **2014**, 50, 15577. (b) Kumar, P.; Prescher, S.; Louie, J. *Angew. Chem., Int. Ed.* **2011**, 50, 10694.
- (15) Hamada, Y.; Matsuura, F.; Oku, M.; Hatano, K.; Shioiri, T. *Tetrahedron Lett.* **1997**, 38, 8961.
- (16) Dierkes, P.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1519.
- (17) Duong, H. A.; Cross, M. J.; Louie, J. *Org. Lett.* **2004**, 6, 4679.
- (18) Dreyer, D. L.; Brenner, R. C. *Phytochemistry* **1980**, 19, 935.
- (19) (a) Schmid, R.; Sapunov, V. N. *Non-Formal Kinetics*; Ebel, H. F., Ed.; Verlag Chemie: Weinheim, 1982; Chapter 3, p 51. (b) Haldane, J. B. S. *Enzymes*; MIT Press Classics: Boston, 1965; Chapter 4, p 84.
- (20) Goertz, W.; Keim, W.; Vogt, D.; Englert, U.; Boele, M. D. K.; van der Veen, L. A.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1998**, 2981.
- (21) Yamamoto, T.; Ishizu, J.; Kohara, T.; Komiya, S.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, 102, 3758.
- (22) For examples of transition metal–isocyanate complexes, see: (a) Antiñolo, A.; Carrillo-Hermosilla, F.; Otero, A.; Fajardo, M.; Garcés, A.; Gómez-Sal, P.; López-Mardomingo, C.; Martín, A.; Miranda, C. *J. Chem. Soc., Dalton Trans.* **1998**, 59. (b) Klein, H.-F.; Helwig, M.; Karnop, M.; König, H.; Hammerschmitt, B.; Cordier, G.; Flörke, U.; Haupt, H.-J. *Z. Naturforsch.* **1993**, 48b, 785.
- (23) Guan, W.; Sakaki, S.; Kurahashi, T.; Matsubara, S. *Organometallics* **2013**, 32, 7564.
- (24) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, 33, 336.