C–H Bond Functionalization

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Mild and Efficient C2-Alkenylation of Indoles with Alkynes Catalyzed by a Cobalt Complex**

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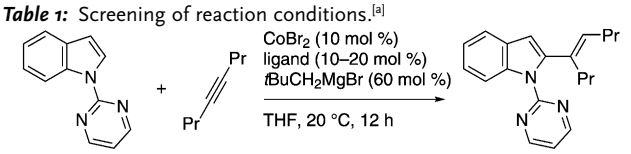
Indole represents a privileged core structural motif that occurs in biologically active natural and unnatural products.[1] Consequently, direct functionalization of the indole nucleus has long attracted interest of synthetic chemists.[2] While the C3-position of indole is the inherently reactive site for Friedel–Crafts-type chemistry,[3] the recent emergence of transition-metal-catalyzed C–H bond functionalization[4] has not only expanded the scope of C3-functionalization but also has opened the door to a variety of methods for C2-functionalization. Nevertheless, compared with arylation,[5,6] catalysts that allow alkenylation of the C2-position are still limited despite the potential utility of such products.[7,8] While disubstituted and trisubstituted olefin products have been accessed by oxidative Heck olefination[9] and hydroarylation of internal alkynes,[10] respectively, there remain significant limitations that warrant further catalyst development, particularly for the latter type of reaction. For example, the nickel catalysis of Nakao, Hiyama et al. needs an electron-withdrawing substituent at the C3-position,[10a,b] while the rhodium catalysis of Schipper, Hutchinson, and Fagnou does not allow the use of dialkylacetylenes.[10c] We report herein efficient C2-alkenylation of indoles bearing an easily removable *N*-pyrimidyl group[11] under room-temperature conditions with a versatile cobalt catalyst. The alkenylated indoles serve as useful platforms for further synthetic manipulations, such as cycloaddition, Friedel–Crafts condensation, and direct C–H functionalization reactions.

With the recent success of cobalt catalysis[12] for aromatic and heteroaromatic C–H bond functionalization demonstrated by us[13,14] and others,[15] we commenced our study with the reaction of *N*-pyrimidylindole **1a** (0.3 mmol) and 4-octyne **2a** (1.5 equiv) in the presence of $CoBr_2$ (10 mol%), ligand (10–20 mol%), and neopentylmagnesium bromide (60 mol%) at 20°C for 12 h (Table 1). Most of the phosphine, N-heterocyclic carbene, and nitrogen ligands that we previously employed for the cobalt catalysis poorly promoted the reaction (Table 1, entries 1–6), except that the use of tris(3-chlorophenyl)phosphine[14f] afforded the desired alkenylation product **3aa** in a moderate yield of 55% but with rather poor mass balance (>90% conversion of **1a**) because of formation of unidentified by-products (Table 1, entry 7).[16] As we reported recently for alkenylation of an aromatic imine,[14f] the use of pyridine (80 mol%) as a coligand accelerated the reaction and modestly improved the product yield (66% with 2 h reaction) yet with unsatisfactory mass balance (Table 1, entry 8). This acceleration effect eventually prompted us to find that a phosphine-pyridine bidentate ligand, 2-(diphenylphosphinoethyl)pyridine (pyphos),[17] effected very clean conversion of the starting materials within two hours,[16] affording **3aa** in 97% yield with exclusive (>50:1) *E* stereochemistry (Table 1, entry 9). Note that the amount of the Grignard reagent (60 mol%) was critical to the catalytic activity, as the reduction of the amount of Grignard reagent led to a significant drop in the product yield (50 mol%, 20%; 40 mol%, 4%; 30 mol%, 1% for 12 h reaction).[18] 1,3-Bis(diphenylphosphino)propane (dppp), a bidentate phosphine that has a bite angle similar to that of the pyphos ligand, was far less effective (Table 1, entry 10). The reaction could be performed on a 5 mmol scale by using 1.2 equiv of **2a** and 5 mol% of the catalyst without significant decrease in the product yield (Table 1, entry 11).

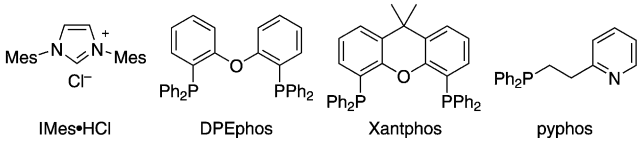
Table 1: Screening of reaction conditions.[a]



1a **2a** (1.5 equiv) **3aa**

Entry	Ligand (mol%)	Yield [%][b]
1	$PMePh_2$ (20)	3
2	PCy_3 (10)	8
3	IMes·HCl (10)	5
4	DPEphos (10)	4
5	Xantphos (10)	13
6	1,10-phenanthroline (10)	1
7	$P(3\text{-}ClC_6H_4)_3$ (20)	55, 24[c]
8	$P(3\text{-}ClC_6H_4)_3$ (20) + pyridine (80)	66[c]
9	pyphos (10)	97,[c] 96[d]
10	dppp (10)	2
11[e]	pyphos (5)	93[d]

[a] Reaction was performed on a 0.3 mmol scale. [b] Determined by GC using *n*-tridecane as an internal standard. [c] Yield obtained at the reaction time of 2 h. [d] Isolated yield. [e] Performed on a 5 mmol scale using 1.2 equiv of **2a** and 5 mol% of the catalyst. Cy = cyclohexyl.



IMes•HCl DPEphos Xantphos pyphos

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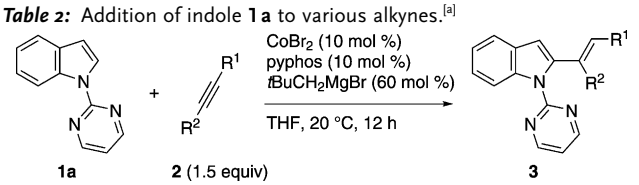
With the effective catalytic system in hand, we moved on to exploration of the scope of the alkenylation reaction. First, addition of **1a** to various alkynes was examined (Table 2). The present reaction tolerated a variety of alkynes including

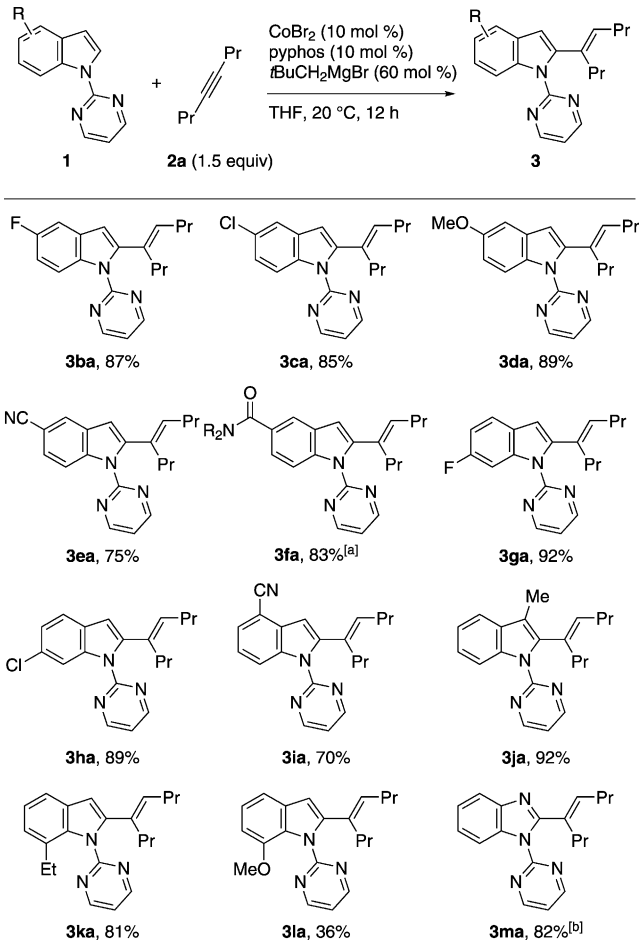
Table 2: Addition of indole **1a** to various alkynes.[a]



1a **2** (1.5 equiv) **3**

Entry	R^1	R^2	**3**	Yield [%][b]	r.r.[c]
1	*n*Pr	*n*Pr	**3aa**	96 (93)	–
2	CH_2SiMe_3	CH_2SiMe_3	**3ab**	88	–
3	*i*Pr	Me	**3ac**	88	8:1
4	*t*Bu	*n*Bu	**3ad**	57	>50:1
5	Ph	Me	**3ae**	91	12:1
6	4-$MeOC_6H_4$	Me	**3af**	89	19:1
7	4-ClC_6H_4	Me	**3ag**	40	13:1
8	Ph	Et	**3ah**	92	1.6:1
9	Ph	*c*-C_3H_5	**3ai**	93	1.4:1
10	2,6-$Me_2C_6H_3$	Et	**3aj**	88	2.5:1
11	Ph	Ph	**3ak**	96 (92)	–
12	$SiMe_3$	Me	**3al**	81	>50:1
13	$SiMe_3$	*n*Bu	**3am**	91	>50:1
14	$SiMe_3$	Ph	**3an**	79	>50:1
15	$SiMe_3$	4-CNC_6H_4	**3ao**	62	>50:1[d]

[a] Reaction was performed on a 0.3 mmol scale. [b] Yield of isolated product. In parentheses the yield of isolated product is shown for a 5 mmol scale reaction using 1.2 equiv of the alkyne and 5 mol% of the catalyst. [c] Regioisomeric ratio determined by ^{1}H NMR spectroscopy. [d] *E*/*Z* ratio was 4:1.

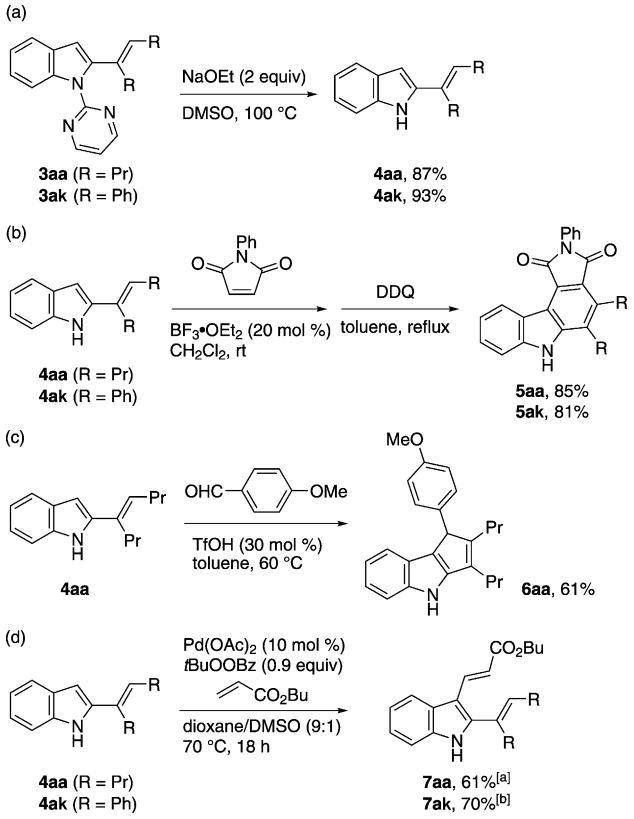


Scheme 1. Addition of various indoles to **2a**. Reaction was performed on a 0.3 mmol scale, and yields of isolated products are shown. [a] NR_2 = morpholino. Reaction time was 40 h. [b] Reaction was performed using 100 mol% of *t*$BuCH_2MgBr$.

dialkyl alkynes (Table 2, entries 1–4), aryl alkyl alkynes (entries 5–10), diphenylacetylene (entry 11), and silyl-substituted alkynes (entries 12–15), and afforded the corresponding alkenylation products in good to excellent yields with exclusive *E* stereochemistry. As was the case with 4-octyne, the reaction of diphenylacetylene was also easily scaled up to 5 mmol scale without problem (Table 2, entry 11). High levels of regioselectivity (8:1 to >50:1) were achieved for alkynes such as 4-methylpent-2-yne, 2,2-dimethyloct-3-yne, 1-aryl-1-propynes, and silyl-substituted alkynes (Table 2, entries 3–7 and 12–15), where the C–C bond formation took place at the less hindered acetylenic carbon atom. However, the sensitivity of the catalyst toward steric change became apparent when the methyl group of 1-phenyl-1-propyne was replaced by an ethyl or a cyclopropyl group (Table 2, entries 8 and 9). Thus, such alkynes exhibited only modest regioselectivity (ca. 1.5:1). The regioselectivity was improved to 2.5:1 by introducing a bulky aryl group (Table 2, entry 10). It is notable that the regioselectivity for 1-aryl-2-trimethylsilylacetylene (Table 2, entries 14 and 15) was the opposite of that observed for the rhodium(III)-catalyzed reaction of *N*-carbamoyl indole.[10c,19]

Next, we explored the reaction of various indole derivatives with 4-octyne **2a** (Scheme 1). *N*-pyrimidyl indoles substituted at the 3–7-positions all participated smoothly in the reaction to afford the corresponding alkenylated products in good to excellent yields. Both electron-withdrawing and -donating substituents, including fluoro (**3ba** and **3ga**), chloro (**3ca** and **3ha**), methoxy (**3da** and **3la**), cyano (**3ea** and **3ia**), tertiary amide (**3fa**), and alkyl (**3ja** and **3ka**) groups could be tolerated. Alkyl substituents at the 3- and 7-positions did not cause any steric inhibition, and the alkenylated products **3ja** and **3ka** were afforded in 92 and 81% yields, respectively. *N*-Pyrimidyl benzimidazole also participated in the reaction with an increased loading of the Grignard reagent (100 mol%) to afford the alkenylated product **3ma** in 82% yield.

Removal of the pyrimidyl group on the alkenylation product was easily achieved by treatment with NaOEt in dimethylsulfoxide (DMSO) at 100 °C,[11] with the stereochemistry of the olefin moiety untouched. Thus, the 4-octyne and diphenylacetylene adducts **3aa** and **3ak** were converted to their free indole derivatives **4aa** and **4ak** in 87 and 93% yields, respectively (Scheme 2a), which served as useful starting materials for further synthetic transformations. First, Diels–Alder reaction of **4aa** and **4ak** with *N*-phenylmaleimide took place smoothly in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$, and the following oxidation using DDQ



Scheme 2. Transformations of 2-alkenylated indoles. [a] A mixture of stereoisomers with respect to the oct-4-en-4-yl group (ratio = 7:1). [b] A mixture of stereoisomers with respect to the 1,2-diphenylethenyl group (ratio = 2:1). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TfOH = trifluoromethanesulfonic acid.

afforded pyrrolocarbazole derivatives **5aa** and **5ak** in 85 and 81% yields, respectively (Scheme 2b).[8] Next, condensation of **4aa** with *p*-anisaldehyde was achieved using TfOH (30 mol%) to afford a 1,4-dihydrocyclopenta[*b*]indole derivative **6aa** in 61% yield (Scheme 2c). This reaction would have proceeded through Friedel–Crafts reaction at the C3-position,[3] Brønsted acid activation of the resulting diarylmethanol, and subsequent intramolecular nucleophilic attack of the alkenyl moiety. Finally, oxidative Heck olefination of the C3-position of **4aa** and **4ak** was achieved by the method developed by Gaunt and co-workers[9a] to afford dialkenylated indoles **7aa** and **7ak** in 61 and 70% yields, respectively (Scheme 2d).

In summary, we have developed a highly efficient, mild, and stereoselective C2-alkenylation reaction of indoles with alkynes catalyzed by a Co–pyphos catalyst. The reaction has significantly broadened the scope of indole C2-alkenylation, and may serve as a complementary method to the reported methods, such as rhodium(III) catalysis.[10c] The high performance of the pyphos ligand may have relevance to the acceleration effect of pyridine on the cobalt-phosphine-catalyzed *ortho* alkenylation of aromatic ketimines that we reported recently,[14f] although mechanistic origin of the acceleration effect remains unclear at present. Systematic studies of the ligand effect on cobalt-catalyzed C–H bond functionalization and their applications to the design of new catalytic systems are currently underway.

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[1] a) R. J. Sundberg, *Indoles*, Academic Press, San Diego, **1996**; b) G. W. Gribble, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1045; c) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2005**, *22*, 73.

[2] a) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2011**, *111*, PR215; b) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608; c) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173; d) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873.

[3] G. A. Olah, R. Khrishnamurti, G. K. S. Prakash in *Comprehensive Organic Synthesis*, *Vol. 3*, 1st ed. (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 293–335.

[4] For recent reviews, see: a) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; b) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885; c) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; e) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, *46*, 677; f) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; g) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; h) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013.

[5] For reviews on transition-metal-catalyzed indole arylation, see: a) L. Joucla, L. Djakovitch, *Adv. Synth. Catal.* **2009**, *351*, 673; b) T. Boorman, I. Larrosa in *Progress in Heterocyclic Chemistry*, *Vol. 22* (Eds.: G. W. Gribble, J. A. Joule), Elsevier, Oxford, **2010**, pp. 1–20.

[6] For selected recent papers on direct C2-arylation of indoles, see: a) N. Lebrasseur, I. Larrosa, *J. Am. Chem. Soc.* **2008**, *130*, 2926; b) S. Kirchberg, R. Fröhlich, A. Studer, *Angew. Chem.* **2009**, *121*, 4299; *Angew. Chem. Int. Ed.* **2009**, *48*, 4235; c) J. Ruiz-Rodríguez, F. Albericio, R. Lavilla, *Chem. Eur. J.* **2010**, *16*, 1124; d) J. Zhou, P. Hu, S. Huang, M. Wang, W. Su, *Chem. Eur. J.* **2010**, *16*, 5876; e) B. Liégault, I. Petrov, S. I. Goresky, K. Fagnou, *J. Org. Chem.* **2010**, *75*, 1047; f) L. Joucla, N. Batail, L. Djakovitch, *Adv. Synth. Catal.* **2010**, *352*, 2929; g) Z. Liang, B. Yao, Y. Zhang, *Org. Lett.* **2010**, *12*, 3185; h) S. Potavathri, K. C. Pereira, S. I. Goresky, A. Pike, A. P. LeBris, B. DeBoef, *J. Am. Chem. Soc.* **2010**, *132*, 14676; i) L. Wang, W.-B. Yi, C. Cai, *Chem. Commun.* **2011**, *47*, 806; j) E. T. Nadres, A. Lazareva, O. Daugulis, *J. Org. Chem.* **2011**, *76*, 471; k) T. Truong, O. Daugulis, *J. Am. Chem. Soc.* **2011**, *133*, 4243; l) S. Yanagisawa, K. Itami, *Tetrahedron* **2011**, *67*, 4425.

[7] For a review on transition-metal-catalyzed alkenylation of heteroarenes, see: R. Rossi, F. Bellina, M. Lessi, *Synthesis* **2010**, 4131.

[8] a) M. Tao, C. H. Park, R. Bihovsky, G. J. Wells, J. Husten, M. A. Ator, R. L. Hudkins, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 938; b) B. D. Palmer, A. M. Thompson, R. J. Booth, E. M. Dobrusin, A. J. Kraker, H. H. Lee, E. A. Lunney, L. H. Mitchell, D. F. Ortwine, J. B. Smaill, L. M. Swan, W. A. Denny, *J. Med. Chem.* **2006**, *49*, 4896.

[9] a) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem.* **2005**, *117*, 3185; *Angew. Chem. Int. Ed.* **2005**, *44*, 3125; b) A. García-Rubia, R. G. Arrayás, J. C. Carretero, *Angew.*

Chem. **2009**, *121*, 6633; *Angew. Chem. Int. Ed.* **2009**, *48*, 6511; c) A. García-Rubia, B. Urones, R. G. Arrayás, J. C. Carretero, *Chem. Eur. J.* **2010**, *16*, 9676; d) E. Capito, J. M. Brown, A. Ricci, *Chem. Commun.* **2005**, 1854; e) A. Maehara, H. Tsurugi, T. Satoh, M. Miura, *Org. Lett.* **2008**, *10*, 1159.

[10] a) Y. Nakao, K. S. Kanyiva, S. Oda, T. Hiyama, *J. Am. Chem. Soc.* **2006**, *128*, 8146; b) K. S. Kanyiva, Y. Nakao, T. Hiyama, *Heterocycles* **2007**, *72*, 677; c) D. J. Schipper, M. Hutchinson, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6910; d) Y. Kuninobu, K. Kikuchi, Y. Tokunaga, K. Takai, *Tetrahedron* **2008**, *64*, 5974; e) W. Lu, C. Jia, T. Kitamura, Y. Fujiwara, *Org. Lett.* **2000**, *2*, 2927; f) R. Gao, C. S. Yi, *J. Org. Chem.* **2010**, *75*, 3144; g) L. L. Suarez, M. F. Greaney, *Chem. Commun.* **2011**, *47*, 7992; h) S. R. Kandukuri, J. A. Schiffner, M. Oestreich, *Angew. Chem.* **2012**, *124*, 1291; *Angew. Chem. Int. Ed.* **2012**, *51*, 1265.

[11] L. Ackermann, A. V. Lygin, *Org. Lett.* **2011**, *13*, 3332.

[12] For recent reviews on cobalt catalysis in organic synthesis, see: a) G. Cahiez, A. Moyeux, *Chem. Rev.* **2010**, *110*, 1435; b) C. Gosmini, A. Moncomble, *Isr. J. Chem.* **2010**, *50*, 568; c) W. Hess, J. Treutwein, G. Hilt, *Synthesis* **2008**, 3537; d) C. Gosmini, J.-M. Bégouin, A. Moncomble, *Chem. Commun.* **2008**, 3221.

[13] N. Yoshikai, *Synlett* **2011**, 1047.

[14] a) K. Gao, P.-S. Lee, T. Fujita, N. Yoshikai, *J. Am. Chem. Soc.* **2010**, *132*, 12249; b) Z. Ding, N. Yoshikai, *Org. Lett.* **2010**, *12*, 4180; c) K. Gao, N. Yoshikai, *J. Am. Chem. Soc.* **2011**, *133*, 400; d) K. Gao, N. Yoshikai, *Angew. Chem.* **2011**, *123*, 7020; *Angew. Chem. Int. Ed.* **2011**, *50*, 6888; e) Z. Ding, N. Yoshikai, *Synthesis* **2011**, 2561; f) P.-S. Lee, T. Fujita, N. Yoshikai, *J. Am. Chem. Soc.* **2011**, *133*, 17283.

[15] a) Q. Chen, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 428; b) L. Ilies, Q. Chen, X. Zeng, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 5221; c) B. Li, Z.-H. Wu, Y.-F. Gu, C.-L. Sun, B.-Q. Wang, Z.-J. Shi, *Angew. Chem.* **2011**, *123*, 1141; *Angew. Chem. Int. Ed.* **2011**, *50*, 1109; d) J. Y. Kim, S. H. Cho, J. Joseph, S. Chang, *Angew. Chem.* **2010**, *122*, 10095; *Angew. Chem. Int. Ed.* **2010**, *49*, 9899; e) Q. Chen, L. Ilies, N. Yoshikai, E. Nakamura, *Org. Lett.* **2011**, *13*, 3232; f) T. Yao, K. Hirano, T. Satoh, M. Miura, *Angew. Chem.* **2012**, *124*, 799; *Angew. Chem. Int. Ed.* **2012**, *51*, 775.

[16] See the Supporting Information for comparison of GC traces of the reactions in entries 7–9.

[17] For examples of the use of the pyphos ligand in catalysis, see: a) E. A. Bercot, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 174; b) Y. Zhang, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 15964.

[18] We suspect that the excess Grignard reagent is necessary to generate a cobalt ate species, which might be responsible for the catalytic activity. See Ref. [14f] for this speculation.

[19] The regio- and stereochemistry of **3an** was confirmed by X-ray crystallographic analysis (see the Supporting Information). CCDC 859819 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

