ORGANIC LETTERS

2012
Vol. 14, No. 2
588–591

Rhenium-Catalyzed Regiodivergent Addition of Indoles to Terminal Alkynes

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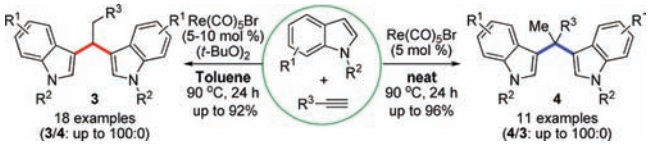
Received December 1, 2011

ABSTRACT



An efficient rhenium-catalyzed site-switchable addition of indoles to terminal alkynes is described. A variety of bisindolylalkane derivatives are expeditiously synthesized in high yields with excellent regioselectivity. Preliminary mechanistic study sheds light on the observed regiodivergent addition.

Indoles are prevalent motifs in a wide range of biologically active molecules, pharmaceuticals, and natural occurring compounds.[1] As a consequence, the synthesis of indole derivatives has attracted comprehensive and continuous interest from chemical communities. Among a myriad of methods to approach functionalized indoles, the direct hydroindolation of alkynes represents one of the most straightforward, highly efficient, and atom-economic strategies to access a variety of indole derivatives.[1,2] Although great success has been achieved in such processes, the control of regioselectivity in the addition of indoles to terminal alkynes is still an important challenge.[3]

To address this issue, activated alkynes containing electron-withdrawing groups such as ester, amide, and sulfone are frequently employed as substrates.[4] Thus, the addition of indoles occurs preferentially in an *anti*-Markovnikov manner due to the biased C−C triple bonds. For the widely occurring unactivated terminal alkynes, however, the Markovnikov addition of indoles has been predominantly developed *via* a variety of transition metal catalysts (Scheme 1, a).[5,6b] The electronic unbalance of the triple bonds in key transition-metal-alkyne complexes is ascribed to govern the regiospecific attack of indoles to the internal C-atom of terminal alkynes, thus resulting in the formation of Markovnikov adducts. In sharp contrast, the *anti*-Markovnikov regioselective addition of indoles to

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(1) For excellent reviews, see: (a) Sundberg, R. J. *Indoles*; Academic Press: London, U.K., 1996. (b) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (c) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (d) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489. (e) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215.

(2) For related reviews on hydroindolations, see: (a) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167. (b) Kirsch, S. F. *Synthesis* **2008**, 3183. (c) Kitamura, T. *Eur. J. Org. Chem.* **2009**, 1111.

(3) For an excellent review, see: Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368.

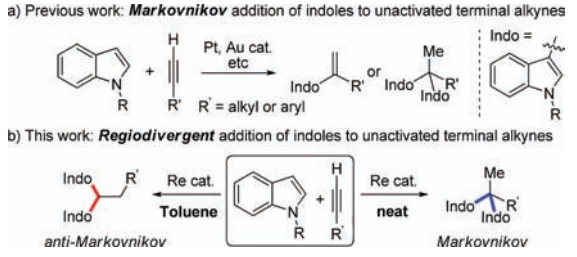
(4) For selected examples, see: (a) Lu, W.; Jia, C.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **2000**, *2*, 2927. (b) Li, Z.; Shi, Z.; He, C. *J. Organomet. Chem.* **2005**, *690*, 5049. (c) Donets, P. A.; Van Der Eycken, E. V.; Hecke, K. V.; Meervelt, L. V. *Org. Lett.* **2009**, *11*, 3618. (d) Li, X.; Wang, J.-Y.; Yu, W.; Wu, L.-M. *Tetrahedron* **2009**, *65*, 1140. (e) Buscemi, G.; Biffis, A.; Tubaro, C.; Basato, M.; Graiff, C.; Tiripicchio, A. *Appl. Organomet. Chem.* **2010**, *24*, 285. (f) Xie, M.-H.; Xie, F.-D.; Lin, G.-F.; Zhang, J.-H. *Tetrahedron Lett.* **2010**, *51*, 1213.

(5) For selected examples, see: (a) Yadav, J. S.; Reddy, B. V. S.; Padmavani, B.; Gupta, M. K. *Tetrahedron Lett.* **2004**, *45*, 7577. (b) Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C.-H. *Chem.—Eur. J.* **2007**, *13*, 8285. (c) Tsuchimoto, T.; Nagase, Y.; Miyamura, T.; Matsubayashi, H.; Kaneko, M.; Shirakawa, E. *J. Am. Chem. Soc.* **2008**, *130*, 15823. (d) Barluenga, J.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *Chem.—Eur. J.* **2009**, *15*, 8121. (e) Cadierno, V.; Francos, J.; Gimeno, J. *Chem. Commun.* **2010**, *46*, 4175. (f) Bhaskar, G.; Saikumar, C.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 3141. (g) Gao, R.; Yi, C. S. *J. Org. Chem.* **2010**, *75*, 3144. (h) Zhang, Y.-Q.; Zhu, D.-Y.; Jiao, Z.-W.; Li, B.-S.; Zhang, F.-M.; Tu, Y.-Q.; Bi, Z. *Org. Lett.* **2011**, *13*, 3458. (i) Tsuchimoto, T.; Kanbara, M. *Org. Lett.* **2011**, *13*, 912. (j) Wang, M.-Z.; Zhou, C.-Y.; Che, C.-M. *Chem. Commun.* **2011**, *47*, 1312.

10.1021/ol203199m
Published on Web 12/29/2011

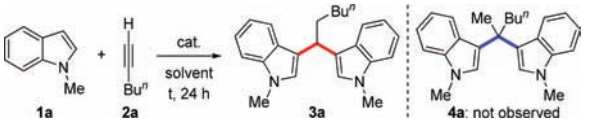
unactivated terminal alkynes is rarely reported.[6] Echavarren et al. elegantly described a Au-catalyzed intramolecular *anti*-Markovnikov hydroindolation of terminal alkynes leading to the formation of six- to eight-membered rings.[6a−c] Barluenga et al. demonstrated that the intermolecular addition of indoles to terminal alkynes bearing a properly positioned hydroxyl "directing group" proceeded in a highly selective *anti*-Markovnikov pattern via Au catalysis.[6d] To the best of our knowledge, intermolecular *anti*-Markovnikov hydroindolation of simple unactivated terminal alkynes without any "directing groups" is still an unmet challenge. Herein, we disclose the first general solution to this challenge by resorting to Re catalysis (Scheme 1b). Also, the regioselectivity can be readily reversed to the Markovnikov pattern while using the same catalyst, which highlights the unique features of Re catalysis.[7,8]

Scheme 1. Intermolecular Hydroindolation of Unactivated Terminal Alkynes



First, the reaction of *N*-methylindole **1a** and 1-hexyne **2a** was examined with a wide range of parameters (Table 1). No conversion was observed with catalysts of $Mn(CO)_5Br$, $Mn_2(CO)_{10}$, or $Re_2(CO)_{10}$ (entry 1−3). To our delight, the *anti*-Markovnikov adduct, bisindolylalkane **3a**, was formed as a single product when $Re(CO)_5X$ (X = Cl, Br) were used as catalysts (entries 4,5). Toluene was the superior solvent (entries 6−10). A higher temperature is detrimental to the reaction presumably due to the decomposition of **3a** (entries 11,12).[9] The increased amount of **2a** and reaction concentration gave the highest conversion of **1a** (entries 13−15). The catalyst loading can be further reduced to 5 mol % while maintaining the same conversion, and **3a** was isolated as a pure product in 89% yield (entry 16). Other variations gave no better results (entries 17−19). Importantly, no Markovnikov adduct **4a** was detected during the screening of reaction conditions. To the best of our knowledge, this represents the first successful example of intermolecular *anti*-Markovnikov addition of indoles to unactivated terminal alkynes without directing groups.

Table 1. Optimization of Reaction Parameters[a]



entry	catalyst (mol %)	**2a** (equiv)	solvent	*t* (°C)	convn (%)[b]
1	$Mn(CO)_5Br$ (10)	1.0	toluene	100	–[c]
2	$Mn_2(CO)_{10}$ (10)	1.0	toluene	100	–[c]
3	$Re_2(CO)_{10}$ (10)	1.0	toluene	100	–[c]
4	$Re(CO)_5Cl$ (10)	1.0	toluene	100	33
5	$Re(CO)_5Br$ (10)	1.0	toluene	100	55
6	$Re(CO)_5Br$ (10)	1.0	xylene	100	46
7	$Re(CO)_5Br$ (10)	1.0	THF	100	–[c]
8	$Re(CO)_5Br$ (10)	1.0	dioxane	100	20
9	$Re(CO)_5Br$ (10)	1.0	DMF	100	–[c]
10	$Re(CO)_5Br$ (10)	1.0	DCE	100	30
11	$Re(CO)_5Br$ (10)	1.0	toluene	120	30
12	$Re(CO)_5Br$ (10)	1.0	toluene	90	60
13	$Re(CO)_5Br$ (10)	1.5	toluene	90	76
14	$Re(CO)_5Br$ (10)	2.0	toluene	90	73
15[d]	$Re(CO)_5Br$ (10)	1.5	toluene	90	92
16[d]	**$Re(CO)_5Br$ (5)**	**1.5**	**toluene**	**90**	**92 (89)**[e]
17[d,f]	$Re(CO)_5Br$ (5)	1.5	toluene	90	68
18[d]	$Re(CO)_5Br$ (5)	1.5	toluene	80	66
19[d]	$Re(CO)_5Br$ (2)	1.5	toluene	90	71

[a] All reactions were carried out on 0.1 mmol scale in 1 mL of solvent for 24 h unless otherwise noted. [b] The conversion of **1a** was determined by ^1H NMR of the reaction mixtures. [c] No conversion was detected. [d] 0.5 mL of toluene. [e] Isolated yield of pure product **3a** on 0.5 mmol scale. [f] Reaction time: 18 h.

With the optimized conditions in hand, the scope of the reaction was investigated with a variety of indoles and alkynes (Table 2). While *N*-H and -acyl indoles afforded no products, *N*-alkyl or -benzyl indoles proved to be suitable substrates for this reaction (entries 1−2). Both electron-donating and -withdrawing substituents on the indole core are well tolerated in this protocol (entries 3−7). It is of note that halogen groups remain intact after the reaction, which leaves easy handles for further synthetic elaborations (entries 5−7). It was observed that many alkyl alkynes with

(6) For intramolecular examples, see: (a) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358. (c) Ferrer, C.; Escribano-Cuesta, A.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 9015. For an intermolecular hydroxyl-directed example, see:(d) Barluenga, J.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *J. Organomet. Chem.* **2009**, *694*, 546.

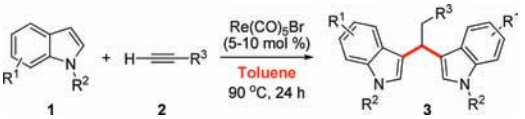
(7) For an excellent review, see: Kuninobu, Y.; Takai, K. *Chem. Rev.* **2011**, *111*, 1938.

(8) For selected examples, see: (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (b) Hua, R.; Tian, X. *J. Org. Chem.* **2004**, *69*, 5782. (c) Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.* **2005**, *7*, 4823. (d) Kusama, H.; Yamabe, H.; Onizawa, Y.; Hoshino, T.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 468. (e) Chung, L. W.; Lee, H. G.; Lin, Z.; Wu, Y.-D. *J. Org. Chem.* **2006**, *71*, 6000. (f) Yudha, S. S.; Kuninobu, Y.; Takai, K. *Org. Lett.* **2007**, *9*, 5609. (g) Takaya, H.; Ito, M.; Murahashi, S.-I. *J. Am. Chem. Soc.* **2009**, *131*, 10824. (h) Saito, K.; Onizawa, Y.; Kusama, H.; Iwasawa, N. *Chem.—Eur. J.* **2010**, *16*, 4716. (i) Kuninobu, Y.; Matsuzaki, H.; Nishi, M.; Takai, K. *Org. Lett.* **2011**, *13*, 2959. (j) Dudle, B.; Rajesh, K.; Blacque, O.; Berke, H. *J. Am. Chem. Soc.* **2011**, *133*, 8168. (k) García-Álvarez, J.; Díez, J.; Gimeno, J.; Seifried, C. M. *Chem. Commun.* **2011**, *47*, 6470. (l) Liu, Q.; Li, Y.-N.; Zhang, H.-H.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *J. Org. Chem.* **2011**, *76*, 1444. (m) Ettedgui, J.; Diskin-Posner, Y.; Weiner, L.; Neumann, R. *J. Am. Chem. Soc.* **2011**, *133*, 188.

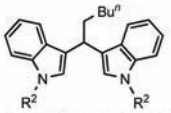
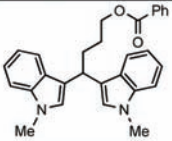
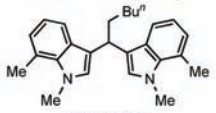
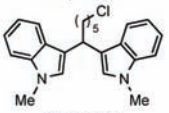
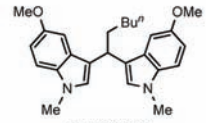
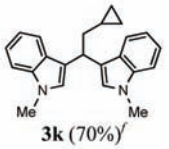
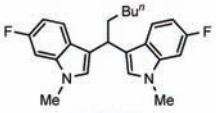
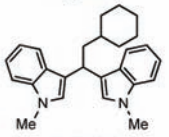
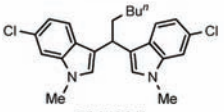
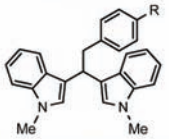
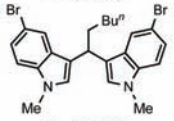
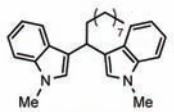
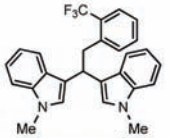
(9) For more details, see Supporting Information (SI).

(10) For cyclopropyl alkyne as a radical clock, see: (a) Back, T. G.; Muralidharan, K. R. *J. Org. Chem.* **1989**, *54*, 121. (b) Gottschling, S. E.; Grant, T. N.; Milnes, K. K.; Jennings, M. C.; Baines, K. M. *J. Org. Chem.* **2005**, *70*, 2686 and references therein.

Table 2. Re-Catalyzed *Anti*-Markovnikov Addition of Indoles to Unactivated Terminal Alkynes[a]



1 2 3

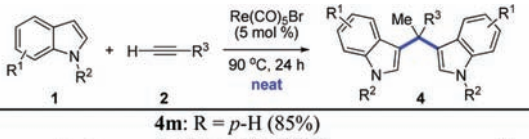
entry	product (yield[b] of **3**, ratio **3**/**4**[c,d])	entry	product (yield[b] of **3**, ratio **3**/**4**[c,d])
1	 **3a**: R^2 = Me (89%)[e]	9	 **3i** (92%)[e]
2	**3b**: R^2 = Bn (70%)		
3	 **3c** (81%)	10	 **3j** (75%)
4	 **3d** (68%)	11	 **3k** (70%)[f]
5	 **3e** (69%)	12	 **3l** (84%)
6	 **3f** (73%)		
7	 **3g** (77%)	13	**3m**: R = H (63%, 11:1)[g]
		14	**3n**: R = Me (66%, 12:1)[h]
		15	**3o**: R = F (63%, 10:1)[i]
		16	**3p**: R = Cl (62%, 7:1)[i]
		17	**3q**: R = CO_2Me (73%)[k]
8	 **3h** (78%)	18	 **3r** (76%)[l]

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), $Re(CO)_5Br$ (0.05 mmol), toluene (2.5 mL), 90 °C, 24 h unless otherwise noted. [b] Isolated yield of pure products **3**. [c] Determined by ^{1}H NMR of the reaction mixtures. [d] No ratio was shown in cases of **3** as the only regioisomers observed. [e] $Re(CO)_5Br$ (0.025 mmol). [f] Reaction on 0.2 mmol scale. [g] **2m** (2.5 mmol), $(t\text{-BuO})_2$ (0.5 mmol), toluene (7.5 mL). [h] **2n** (2 mmol), $(t\text{-BuO})_2$ (0.8 mmol), toluene (3.5 mL). [i] **2o** (2 mmol), $(t\text{-BuO})_2$ (0.5 mmol), toluene (5 mL). [j] **2p** (2 mmol), $(t\text{-BuO})_2$ (1.0 mmol), toluene (5 mL). [k] $(t\text{-BuO})_2$ (0.5 mmol), toluene (5 mL). [l] Toluene (1.5 mL).

linear or cyclic functional groups are amenable to this protocol leading to **3** in good to excellent yields (entries 8–12). It is worth pointing out that no ring-opened product was found when a radical clock type substrate, cyclopropylacetylene **2k**, was employed, which implies a radical pathway of the addition may not be possible (entry 11).[10] Remarkably, all the reactions of alkylacetylenes with indoles proceed in a sole *anti*-Markovnikov fashion. Phenylacetylene derivatives proved to be more challenging substrates; however, good to perfect levels of regiocontrol can be obtained by subtle tuning of the reaction conditions and/or with the presence of a di-*tert*-butyl peroxide additive, which presumably provides weak coordination to the Re center of the active catalyst (entries 13–18).[9]

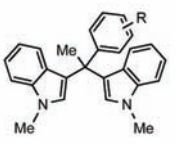
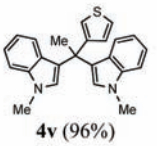
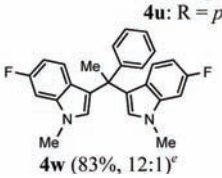
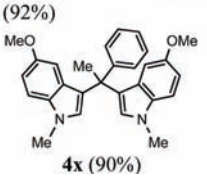
During the survey of reaction parameters for aromatic alkynes, it occurred to us that the reaction concentration is very crucial for the site selectivity of the addition.[9] Surprisingly, the regioselectivity of the reaction can be greatly reoriented to the Markovnikov pattern favoring the formation of bisindolylalkane **4** when the reaction was undertaken simply under *neat* conditions (Scheme 2). Specifically, indole **1a** reacted with phenylacetylene in the absence of toluene affording Markovnikov adduct **4m** in excellent yield while no formation of *anti*-Markovnikov product **3m** was observed. An array of alkynes bearing electron-varied and synthetically useful groups, such as methyl, methoxyl, halo, and ester, is well tolerated under the reaction conditions (**4n**–**u**). 3-Thienylacetylene, as an example of heteroaromatic alkyne, is also amenable to this protocol (**4v**). Also, indoles containing electron-withdrawing or -donating substituents also work giving rise to the corresponding Markovnikov adducts (**4w**–**x**). Notably, both the Markovnikov and *anti*-Markovnikov additions are promoted by the same Re catalyst, [$Re(CO)_5Br$], which features a superb regiodiverse selectivity under the slightly different reaction conditions (e.g., Table 2, **3q** vs Scheme 2, **4q**).

Scheme 2. Re-Catalyzed Markovnikov Addition of Indoles to Unactivated Terminal Alkynes[a–c]



1 2 4

4m: R = *p*-H (85%)
4n: R = *p*-Me (95%)
4o: R = *p*-F (92%)
4p: R = *p*-Cl (82%)
4q: R = *p*-CO_2Me (88%)[d]
4s: R = *m*-Cl (71%)
4t: R = *p*-Br (72%)
4u: R = *p*-OMe (92%)

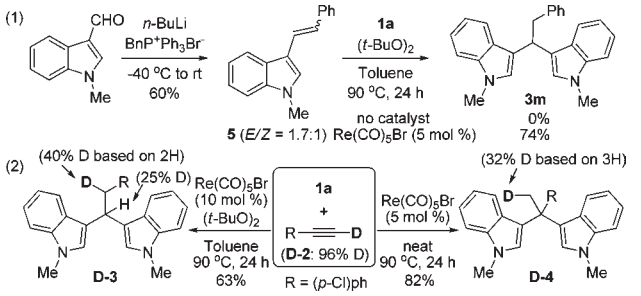


4v (96%)

4w (83%, 12:1)[e]

4x (90%)

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), $Re(CO)_5Br$ (0.025 mmol), neat, 90 °C, 24 h. [b] Isolated yield of pure products **4**. [c] Only products **4** were observed unless otherwise noted. [d] Toluene (0.1 mL) was added. [e] The ratio of **4w**/**3w** was listed in brackets and determined by ^{1}H NMR of the reaction mixtures.

To probe the reaction mechanism, several insightful experiments were undertaken. First, 3-styrylindole **5** was synthesized *via* Wittig olefinnation and then treated with

indole **1a** under aforementioned conditions (Scheme 3, eq 1). It was found that **3m** was obtained in 74% conversion implying 3-styrylindole **5** might be the possible reaction intermediate. Furthermore, no conversion was observed in the absence of a Re catalyst demonstrating its essential role in this hydroindolation step. Second, deuterium-labeled *p*-chlorophenylacetylene **D-2** was employed to react with **1a** in order to investigate the possible pathways underlying the distinct regioselectivity (eq 2). It was shown that D-atom remains intact in the Markovnikov adduct **D-4** (eq 2, right). In contrast, the incorporation of 40% D-atom on the benzylic carbon of adduct **D-3** was found indicating alternative pathways might operate in the *anti*-Markovnikov addition reactions (eq 2, left).[9]

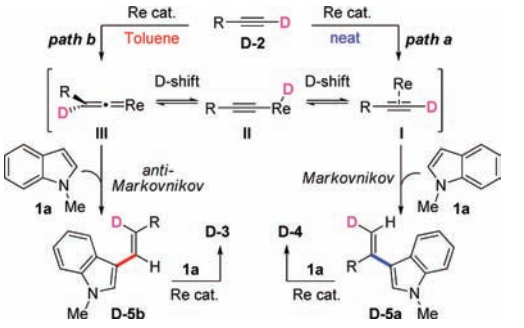
Scheme 3. Investigations on the Reaction Mechanism



On the basis of these results, plausible mechanisms are proposed though the detailed reaction pathways are still unclear at this stage (Scheme 4). Coordination of Re with alkyne **D-2** affords intermediate **I** (*path a*). Under the neat reaction conditions, direct nucleophilic attack of **1a** on the internal carbon of the C−C triple bond leads to the formation of 3-alkenylindole **D-5a**. Note that the regioselectivity in this step is frequently observed in other transition-metal catalyzed hydroindolations of alkynes.[5] Subsequently, the second hydroindolation of **D-5a** promoted by a Re catalyst gives the final Markovnikov product **D-4**. Yet, the 1,2- or 1,3-shift of the D-atom in intermediate **I** or **II** respectively might take place preferentially leading to Re-vinylidene **III** when the reaction was conducted under the dilute solution of toluene (*path b*).[11] The nucleophilic attack of indole **1a** on the carbon α to the Re center of **III** followed by protonolysis affords 3-alkenylindole **D-5b**. Similarly, the *anti*-Markovnikov adduct **D-3** was eventually

(11) For leading reviews on the catalysis involving metal-vinylidenes, see: (a) Bruneau, C.; Dixneuf, P. *Metal Vinylidenes and Allenylidenes in Catalysis*; Wiley-VCH: Weinheim, Germany, 2008. (b) Trost, B. M.; McClory, A. *Chem.—Asian J.* **2008**, *3*, 164.

Scheme 4. A Plausible Mechanism Diagram



obtained through the second Re-catalyzed hydroindolation process.[9]

In summary, the first general procedure for the intermolecular *anti*-Markovnikov addition of indoles to unactivated terminal alkynes was successfully developed *via* Re catalysis. Furthermore, the site selectivity of the addition can be readily reversed to the Markovnikov pattern by subtle tuning of the reaction conditions. Thus, a wide spectrum of regioisomeric bisindolylalkanes are expeditiously synthesized in high yield with excellent selectivity.[12] Preliminary mechanistic study showed that the involvement of key Re-alkyne complexes or Re-vinylidene intermediates might account for the observed regiodiverse selectivity. Further studies on the reaction mechanism and related Re-catalyzed transformations are underway in our laboratory.

Acknowledgment. Generous financial support from the National Science Foundation of China (21002103) and Institute of Chemistry, CAS is gratefully acknowledged. We also thank Prof. Zhenfeng Xi (Peking University) for sustained support.

Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) For selected examples of bisindolylalkanes in natural occurring compounds and of biological and pharmacological importance, see: (a) Garbe, T. R.; Kobayashi, M.; Shimizu, N.; Takesue, N.; Ozawa, M.; Yukawa, H. *J. Nat. Prod.* **2000**, *63*, 596. (b) Veluri, R.; Oka, I.; Wagner-Dobler, I.; Laatsch, H. *J. Nat. Prod.* **2003**, *66*, 1520. (c) Bowman, A. L.; Nikolovska-Coleska, Z.; Zhong, H.; Wang, S.; Carlson, H. A. *J. Am. Chem. Soc.* **2007**, *129*, 12809. (d) Noguchi-Yachide, T.; Tetsuhashi, M.; Aoyama, H.; Hashimoto, Y. *Chem. Pharm. Bull.* **2009**, *57*, 536. (e) Giannini, G.; Marzi, M.; Marzo, M. D.; Battistuzzi, G.; Pezzi, R.; Brunetti, T.; Cabri, W.; Vesci, L.; Pisano, C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2840. (f) Cai, S.-X.; Li, D.-H.; Zhu, T.-J.; Gu, Q.-Q.; Wang, F.-P.; Xiao, X. *Helv. Chim. Acta* **2010**, *93*, 791.