JOC The Journal of Organic Chemistry

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$RuH_2(CO)(PPh_3)_3$ Catalyzed Selective Formation of 1,4-Disubstituted Triazoles from Cycloaddition of Alkynes and Organic Azides

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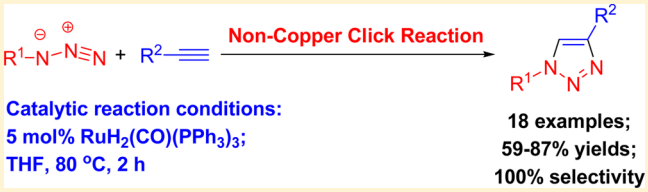
Supporting Information

ABSTRACT: The ruthenium hydride complex $RuH_2(CO)(PPh_3)_3$ was found to be an effective catalyst for the cycloaddition reactions of terminal alkynes and azides. In the presence of $RuH_2(CO)(PPh_3)_3$, various azides reacted with a range of terminal alkynes to produce 1,4-disubstituted 1,2,3-triazoles with 100% selectivity and moderate to excellent yields.



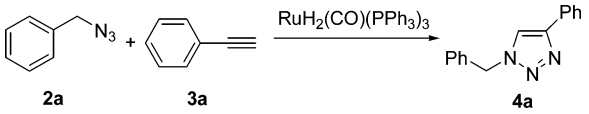
Huisgen's 1,3-dipolar cycloaddition of azides and alkynes is the most straightforward route to give 1,2,3-triazoles[1] and was thoroughly studied in the 1950−1970s.[2] The cycloaddition is highly exothermic, but it often proceeds very slowly even at elevated temperature (80−120 °C for 12−24 h)[3] because of the high activation barrier (ca. 25−26 kcal/mol for reaction of methyl azide with propyne).[4] As another distinct disadvantage, the cycloaddition of azide and unsymmetrically substituted alkyne usually affords a mixture of regioisomers. The discovery of Cu(I)-catalyzed azide−alkyne cycloaddition (CuAAC) yielding selectively 1,4-disubstituted 1,2,3-triazoles is a very important advance in the chemistry of 1,2,3-triazoles.[5] As the most powerful Click reaction which fosters the area of Click chemistry, CuAAC has been successfully applied in wide areas including organic synthesis, chemical biology, drug development, and materials sciences.[6] However, effective noncopper catalysts for the cycloaddition of alkynes and azides are still very rare.[7] Very recently, charcoal impregnated with zinc was described as an effective catalyst for the cycloaddition of arylazides and alkynes to afford the 1,4-disubstituted 1,2,3-triazoles.[8]

Recently, we[9] and others[10] developed a facile cycloaddition of a wide range of azides and terminal alkynes with pentamethylcyclopentadienyl ruthenium chloride complexes as the effective catalysts for azide−alkyne cycloaddition (RuAAC), which complementarily affords the 1,5-disubstituted 1,2,3-triazoles with high regioselectivity. Applications of this RuAAC, although not as widely as those of CuAAC, have also been reported in the literature.[11] As a successive endeavor to explore the ruthenium-catalyzed "Click reaction", we report herein that ruthenium complex $RuH_2(CO)(PPh_3)_3$ can catalyze the cycloaddition of a range of azides and alkynes to afford 1,4-disubstituted 1,2,3-triazoles with 100% selectivity.

We have previously briefly mentioned that ruthenium(II) complexes lacking cyclopentadienyl ligands, such as $RuCl_2(PPh_3)_3$, $RuHCl(CO)(PPh_3)_3$, $RuH_2(CO)(PPh_3)_3$, and $Ru(OAc)_2(PPh_3)_2$, can catalyze the cycloaddition of benzyl azide and phenylacetylene to give selectively 1,4-substituted triazole regioisomer in low yields. $RuH_2(CO)(PPh_3)_3$ (**1**) is the most active one.[9] Encouraged by the observation, we have optimized the reaction catalyzed by $RuH_2(CO)(PPh_3)_3$ using the cycloaddition of benzyl azide and phenylacetylene as the prototype reaction. In the screening experiments, a mixture of benzyl azide (**2a**) and phenylacetylene (**3a**) in THF was heated at 80 °C for 2 h in the presence of 5 mol % of $RuH_2(CO)(PPh_3)_3$. The resulting reaction mixture was then analyzed by ^1H NMR with $PhSiMe_3$ as the internal standard, and the results are given in Table 1. The reaction of **2a** and **3a** catalyzed by complex **1** carried out in hexane gave low conversion due to the poor solubility of the catalyst (Table 1, entry 1). The protic solvent CH_3OH has a negative effect on the reaction, and only 43% yield was obtained (Table 1, entry 2). In aprotic solvents such as CH_3NO_2, CH_3CN, 1,2-dichloroethane (DCE), DMSO, and dioxane, the reaction worked well to afford the triazole product **4a** in 67−76% yields (Table 1, entries 3−7). When the reactions were performed in benzene and THF, the 1,4-disubstituted 1,2,3-triazole **4a** was obtained in 79% yield (Table 1, entries 8 and 9). If the ratio of **2a** to **3a** was changed from 1:2 to 1:1, 1:1.1, or 2:1, the reaction yield was decreased slightly (Table 1, entries 10−12). It is noted that the catalytic reaction could not proceed at room temperature, however. Different from the RuAAC via the ruthenacycle intermediate, which controls the regioselectivity to afford the 1,5-disubstituted 1,2,3-triazoles,[9] the current reaction affording regioselectively the 1,4-disubstituted 1,2,3-triazoles undergoes the mechanism via the ruthenium acetylide as the key intermediate, which is proved by the experimental fact that the ruthenium complex $Ru(CO)(C{\equiv}CBu\text{-}t)_2(PPh_3)_3$ is also the effective catalyst for

Received: May 2, 2012
Published: June 6, 2012

Table 1. Cycloaddition of Benzyl Azide and Phenylacetylene Catalyzed by $RuH_2(CO)(PPh_3)_3$[a]



2a 3a 4a

entry	solvent	2a:3a	conv (%)[b]	yield (%)[c]
1	hexane	1:2	38	<5
2	CH_3OH	1:2	100	43
3	CH_3NO_2	1:2	100	67
4	CH_3CN	1:2	100	69
5	DCE	1:2	100	71
6	DMSO	1:2	100	75
7	dioxane	1:2	99	76
8	benzene	1:2	97	79
9	THF	1:2	100	79 (82)[d]
10[e]	THF	1:1.1	100	73
11[f]	THF	1:1	100	76
12[g]	THF	2:1	100	74

[a]General reaction conditions: **2a** (0.5 mmol), **3a** (1.0 mmol), $RuH_2(CO)(PPh_3)_3$ (0.025 mmol), 80 °C, 2 h, 0.5 mL of solvent was added unless otherwise noted. [b]The conversions were estimated on the basis of the integration of triazole and unreacted azide in ^1H NMR spectra. [c]Based on azide (**2a**) used, determined by ^1H NMR integration using $PhSiMe_3$ as the internal standard. [d]The yield in the parentheses is the isolate yield. [e]**2a** (0.5 mmol) and **3a** (0.55 mmol) were used. [f]**2a** (0.5 mmol) and **3a** (0.5 mmol) were used. [g]**2a** (1.0 mmol) and **3a** (0.5 mmol) were used.

this cycloaddition to produce regioselectively the 1,4-disubstituted 1,2,3-triazoles.

Subsequently, the cycloaddition reactions of various azides and a series of alkynes were examined in THF at 80 °C (oil bath temperature), using 5 mol % $RuH_2(CO)(PPh_3)_3$ (**1**) as the catalyst (Table 2). The triazole products were isolated after 2 h, and their structures are fully consistent with their ^1H, $^{13}C\{^1H\}$ NMR, and HRMS data. The reactions of benzyl azide **2a** with aromatic alkynes **3a**−**3g** all proceeded to selectively afford the 1,4-substituted triazole products (Table 2, entries 1−7). In most of the reactions, the expected triazoles were obtained in 81−87% isolated yields. The reaction of **2a** with **3d** bearing the coordinating NH_2 group gave a slightly lower yield of 70% (Table 2, entry 4). The presence of electron-withdrawing groups such as acetyl or ester groups in the arylacetylene has a negative effect, and the product yields are 59 and 62%, respectively (Table 2, entries 6 and 7). The cycloaddition of **2a** with ferrocenyl acetylene **3h** proceeded smoothly, giving the corresponding triazole in 82% yield (Table 2, entry 8). When alkenyl alkyne **3i** was used as the substrate, its cycloaddition with **2a** gave the product **4i** in 69% yield (Table 2, entry 9). Aliphatic alkynes containing an OH or CN group also showed good reactivities with **2a**, and the yields of the products **4j** and **4k** are comparable to those from the reactions of aromatic alkynes (Table 2, entries 10 and 11). The reaction of **2a** with the alkyne **3l** having a more sterically hindered cyclohexyl group produced the triazole product **4l** with a slightly decreased yield of 61% (Table 2, entry 12). We noted that the reaction of **2a** with the sterically hindered *tert*-butylacetylene afforded the triazole product in a very low yield (11%).

We also explored the scope of azides in the cycloaddition reactions. The azides **2b** and **2c** bearing a methyl or iodine group in the aromatic ring also readily reacted with phenylacetylene **3a** to afford the corresponding 1,4-substituted triazoles **4m** and **4n** in 76 and 81% yields, respectively (Table 2, entries 13 and 14). The reactions of the aliphatic azides **2d**−**2f** with **3a** also proceeded smoothly to produce the products **4o**−**4q** in good yields (Table 2, entries 15−17). It is noteworthy that a very low yield of 9% was obtained in the cycloaddition reaction of *p*-tolylazide with phenylacetylene and that the cycloaddition of azides with internal alkynes failed to afford the products under the typical reaction conditions. In general, aryl azides are less stable than their aliphatic counterparts and are prone to react with the ruthenium catalyst to form the ruthenium imido complexes, which is proposed to be the main reason for the reactivity decrease in the RuAAC.[9] Podophyllotoxin and its derivatives exhibit pronounced biological activity mainly as antineoplastic drugs and antiviral agents.[12] As an application of the 1,4-RuAAC in natural product derivation, the podophyllotoxin-based azide **2g** reacted with phenylacetylene **3a** in toluene in the presence of 10 mol % of complex **1** to give the triazole product **4r** in 74% yield (Table 2, entry 18). It is noteworthy that in current investigated substrate scope, the cycloaddition of azides with alkynes catalyzed by $RuH_2(CO)(PPh_3)_3$ has demonstrated 100% selectivity to afford the 1,4-disubstituted 1,2,3-triazoles, and no 1,5-disubstituted 1,2,3-triazoles could be detected. The current RuAAC affords the same products with CuAAC, but the ruthenium catalyst $RuH_2CO(PPh_3)_3$ has more versatile catalytic ability compared with Cu^+ catalyst used in CuAAC. $RuH_2(CO)(PPh_3)_3$ has been described to be the effective catalyst for multiple reactions including C−C coupling, C−H activation, C−O bond cleavage, transfer hydrogenation, cycloaddition and hydrogen transfer reactions, etc. So, the ruthenium catalyst might act as the bifunctional or multifunctional catalyst to fulfill more transformations accompanying the RuAAC in one pot. For example, the reaction of **2a** and **3f** in the presence of 1,4-butanediol was carried out with $RuH_2(CO)(PPh_3)_3$ as the catalyst, and the compound **4s** was obtained as the product of both RuAAC and transfer hydrogenation (Table 2, entry 19). In contrast, the reactions using $CuSO_4$/sodium ascorbate, CuI, or $CuBr(PPh_3)_3$ as the catalysts under similar conditions only produced the cycloaddition product **4f**, and no **4s** was detected. As the possible advantage compared with the traditional CuAAC, more one-pot reactions or tandem reactions based on this RuAAC might be exploited with the ruthenium complex as the catalyst in the future.

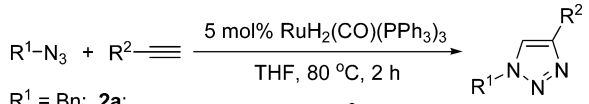
In summary, the catalytic activity of $RuH_2(CO)(PPh_3)_3$ has been evaluated for the cycloaddition of terminal alkynes and azides to give selectively 1,4-disubstituted 1,2,3-triazoles. With $RuH_2(CO)(PPh_3)_3$ as the catalyst, various azides readily reacted with a range of terminal alkynes to produce 1,4-disubstituted 1,2,3-triazoles with 100% selectivity and moderate to excellent yields. This is the first report describing a catalytic system of noncopper metal complexes for the cycloaddition of azides with terminal alkynes to selectively produce 1,4-disubstituted 1,2,3-triazoles. The current results together with those mediated by pentamethylcyclopentadienyl ruthenium chloride complexes (which afford the 1,5-disubstituted 1,2,3-triazoles) provide an interesting example of dramatic ligand effect on the selectivity of catalytic reactions. Further investigations for the reaction mechanism and the possible one-pot or tandem reactions based on this RuAAC are undergoing in our laboratories.

■ EXPERIMENTAL SECTION

All manipulations were carried out under a nitrogen atmosphere using standard Schlenk techniques, unless otherwise stated. Solvents were distilled under nitrogen from sodium-benzophenone (hexane, diethyl

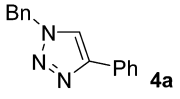
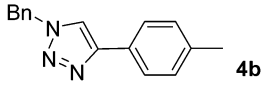
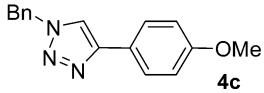
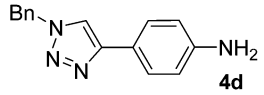
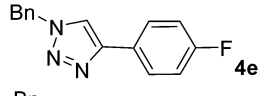
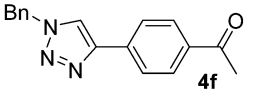
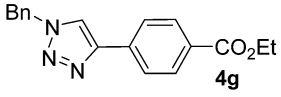
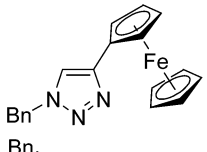
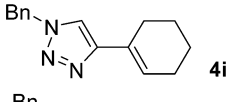
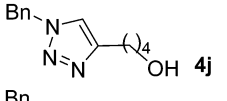
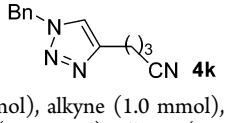
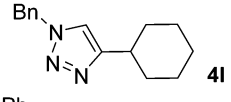
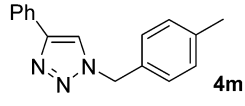
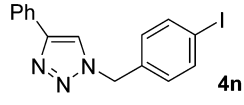
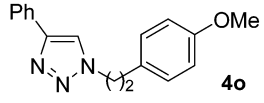
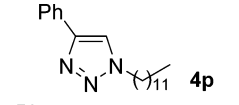
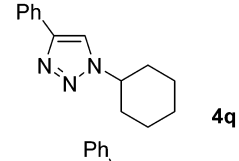
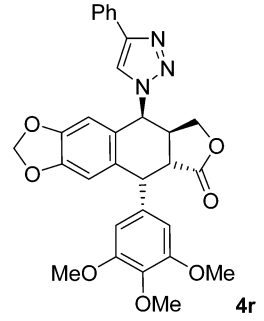
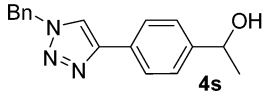
dx.doi.org/10.1021/jo3008572 | J. Org. Chem. 2012, 77, 5844−5849

Table 2. Cycloaddition of Azides and Various Alkynes Using Complex 1 as the Catalyst[a]



R^1 = Bn: **2a**;
4-Me-Ph-CH_2: **2b**;
4-I-Ph-CH_2: **2c**;
4-MeO-Ph-CH_2CH_2: **2d**;
$CH_3(CH_2)_{10}CH_2$: **2e**;
cyclohexyl: **2f**;
1-podophyllotoxin: **2g**;

R^2 = Ph: **3a**;
4-Me-Ph-CH_2: **3b**;
4-MeO-Ph-CH_2: **3c**;
4-NH_2-Ph-CH_2: **3d**;
4-F-Ph-CH_2: **3e**;
4-CH_3CO-Ph-CH_2: **3f**;
4-$EtCO_2$-Ph-CH_2: **3g**;
ferrocenyl: **3h**;
cyclohexenyl: **3i**;
HO-$(CH_2)_3CH_2$: **3j**;
NC-$(CH_2)_2CH_2$: **3k**;
cyclohexyl: **3l**;

entry	azide	alkyne	product	Yield (%)[b]
1	**2a**	**3a**	 **4a**	82
2	**2a**	**3b**	 **4b**	84
3	**2a**	**3c**	 **4c**	87
4	**2a**	**3d**	 **4d**	70
5	**2a**	**3e**	 **4e**	81
6	**2a**	**3f**	 **4f**	59
7	**2a**	**3g**	 **4g**	62
8	**2a**	**3h**	 **4h**	82
9	**2a**	**3i**	 **4i**	69
10	**2a**	**3j**	 **4j**	84
11	**2a**	**3k**	 **4k**	71
12	**2a**	**3l**	 **4l**	61
13	**2b**	**3a**	 **4m**	76
14	**2c**	**3a**	 **4n**	81
15	**2d**	**3a**	 **4o**	78
16	**2e**	**3a**	 **4p**	79
17	**2f**	**3a**	 **4q**	75
18[c]	**2g**	**3a**	 **4r**	74
19[d]	**2a**	**3f**	 **4s**	46

[a]Reaction conditions: azide (0.5 mmol), alkyne (1.0 mmol), $RuH_2CO(PPh_3)_3$ (0.025 mmol), 80 °C, 2 h, 0.5 mL of THF unless noted. [b]Isolated yields. [c]Reaction conditions: azide (0.5 mmol), alkyne (1.0 mmol), $RuH_2CO(PPh_3)_3$ (0.050 mmol), 80 °C, 6 h, 0.5 mL of toluene. [d]Reaction conditions: azide (0.5 mmol), alkyne (1.0 mmol), 1,4-butanediol (4.0 mmol), $RuH_2CO(PPh_3)_3$ (0.025 mmol), 120 °C, 48 h, 0.5 mL of toluene.

ether, THF, benzene) or calcium hydride (dichloroethane). The organic azides **2a**–**2f**,[13] **2g**,[14] alkynes **3f**, **3g**,[15] and $RuH_2(CO)(PPh_3)_3$ (**1**)[16] were prepared according to literature methods. Chemical shifts (δ, ppm) in the ^1H NMR spectra were recorded using TMS as internal standard. Chemical shifts in $^{13}C\{^1H\}$ NMR spectra were internally referenced to $CHCl_3$ (δ = 77.0 ppm).

dx.doi.org/10.1021/jo3008572 | J. Org. Chem. 2012, 77, 5844–5849

Typical Procedure for the Cycloaddition of Alkyne with Azide. To a mixture of azide (0.5 mmol), alkyne (1.0 mmol), and THF (0.5 mL) was added the catalyst $RuH_2(CO)(PPh_3)_3$ (23.4 mg, 0.025 mmol). The resulting solution was stirred at 80 °C for 2 h. The solvent was evaporated under reduced pressure, and the residue was passed through flash column chromatography on silica gel to afford the desired product. **4f**, **4g**, **4o**, and **4s** are new compounds, and the other products **4a**−**4e**, **4h**−**4n**, **4p**−**4r** are known compounds.

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (4a).[8a] The compound was prepared from **2a** (0.067 g, 0.5 mmol) and **3a** (0.102 g, 1.0 mmol) following typical procedure: 0.096 g (82% yield) of product was obtained after column chromatography (eluent = petroleum ether/ethyl acetate 3:1 v/v); mp 127−129 °C (lit. 126−128 °C);[8a] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.79 (d, J = 8.0 Hz, 2H), 7.66 (s, 1H), 7.28−7.40 (m, 8H), 5.55 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 148.1, 134.6, 130.4, 129.1, 128.7, 128.1, 128.0, 125.6, 119.5, 54.1; MS (+CI) m/z (%) 236.13 (M + H$^+$, 100).

1-Benzyl-4-*p*-tolyl-1*H*-1,2,3-triazole (4b).[17] The compound was prepared from **2a** (0.067 g, 0.5 mmol) and **3b** (0.116 g, 1.0 mmol) following typical procedure: 0.105 g (84% yield) of product was obtained after column chromatography (eluent = petroleum ether/ethyl acetate 4:1 v/v); mp 151−153 °C (lit. 155−157 °C);[17] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.67 (d, J = 8.1 Hz, 2H), 7.61 (s, 1H), 7.24−7.37 (m, 5H), 7.18 (d, J = 8.0 Hz, 2H), 5.52 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 148.1, 137.9, 134.7, 129.4, 129.0, 128.6, 127.9, 127.6, 125.5, 119.1, 54.0, 21.1; MS (+CI) m/z (%) 249.98 (M + H$^+$, 100).

1-Benzyl-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (4c).[17] The compound was prepared from **2a** (0.067 g, 0.5 mmol) and **3c** (0.132 g, 1.0 mmol) following typical procedure: 0.115 g (87% yield) of product was obtained after column chromatography (eluent = petroleum ether/ethyl acetate 4:1 v/v); mp 140−142 °C (lit. 144−146 °C);[17] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.70−7.72 (m, 2H), 7.58 (s, 1H), 7.34−7.37 (m, 3H), 7.28−7.30 (m, 2H), 6.91−6.93 (m, 2H), 5.53 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 159.2, 148.0, 134.7, 129.0, 128.6, 128.0, 126.9, 123.2, 118.7, 114.1, 55.2, 54.1; MS (+CI) m/z (%) 266.13 (M + H$^+$, 100).

4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)benzenamine (4d).[17] The compound was prepared from **2a** (0.067 g, 0.5 mmol) and **3d** (0.117 g, 1.0 mmol) following typical procedure: 0.088 g (70% yield) of product was obtained after column chromatography (eluent = CH_2Cl_2/CH_3OH 25:1 v/v); mp 177−179 °C (lit. 182−185 °C);[17] ^{1}H NMR (400 MHz, CD_3CN, 25 °C) δ 7.90 (s, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.32−7.39 (m, 5H), 6.68 (d, J = 8.4 Hz, 2H), 5.54 (s, 2H), 4.28 (br, 2H); ^{13}C NMR (100.6 MHz, CD_3CN, 25 °C) δ 149.1, 137.1, 129.9, 129.3, 128.9, 127.5, 121.0, 120.0, 118.3, 115.5, 54.5; MS (+CI) m/z (%) 251.13 (M + H$^+$, 100).

1-Benzyl-4-(4-fluorophenyl)-1*H*-1,2,3-triazole (4e).[8a] The compound was prepared from **2a** (0.067 g, 0.5 mmol) and **3e** (0.120 g, 1.0 mmol) following typical procedure: 0.103 g (81% yield) of product was obtained after column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v); mp 108−110 °C (lit. 106−108 °C);[8a] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.73−7.77 (m, 2H), 7.64 (s, 1H), 7.26−7.37 (m, 5H), 7.04−7.08 (m, 2H), 5.54 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 163.7, 161.3, 147.2, 134.5, 129.0, 128.7, 127.9, 127.4, 127.3, 126.7, 119.3, 115.8, 115.5, 54.1; MS (+CI) m/z (%) 254.10 (M + H$^+$, 100).

1-(4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)phenyl)ethanone (4f). The compound was prepared from **2a** (0.067 g, 0.5 mmol) and **3f** (0.144 g, 1.0 mmol) following typical procedure: 0.082 g (59% yield) of product was obtained as amorphous solid after column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v); mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.00 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H), 7.75 (s, 1H), 7.39−7.42 (m, 3H), 7.33−7.34 (m, 2H), 5.60 (s, 2H), 2.62 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 197.6, 147.1, 136.5, 135.0, 134.4, 129.3, 129.0, 128.9, 128.2, 125.6, 120.4, 54.4, 26.6; HRMS (ESI, TOF) calcd for $C_{17}H_{16}N_3O$ [M + H]$^+$ 278.1293, found 278.1292.

Ethyl 4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)benzoate (4g). The compound was prepared from **2a** (0.067 g, 0.5 mmol) and **3g** (0.174 g, 1.0 mmol) following typical procedure: 0.095 g (62% yield) of product was obtained as amorphous solid after column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v); mp 124−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.08 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.74 (s, 1H), 7.39−7.41 (m, 3H), 7.32−7.34 (m, 2H), 5.60 (s, 2H), 4.38 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 166.3, 147.2, 134.7, 134.4, 130.2, 129.9, 129.3, 128.9, 128.2, 125.4, 120.4, 61.1, 54.4, 14.4; HRMS (ESI, TOF) calcd for $C_{18}H_{18}N_3O_2$ [M + H]$^+$ 308.1399, found 308.1394.

1-Benzyl-4-ferrocenyl-1,2,3-triazole (4h).[18] The compound was prepared from **2a** (0.067 g, 0.5 mmol) and **3h** (0.211 g, 1.0 mmol) following typical procedure: 0.141 g (82% yield) of product was obtained after column chromatography (eluent = CH_2Cl_2); mp 151−153 °C (lit. 145−147 °C);[18] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.27−7.38 (m, 6H), 5.52 (s, 2H), 4.69 (s, 2H), 4.28 (s, 2H), 4.06 (s, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 147.2, 134.9, 129.0, 128.6, 127.8, 118.7, 75.4, 69.5, 68.6, 66.6, 54.0; MS (+CI) m/z (%) 344.21 (M + H$^+$, 100).

1-Benzyl-4-cyclohexenyl-1*H*-1,2,3-triazole (4i).[19] The compound was prepared from **2a** (0.067 g, 0.5 mmol) and **3i** (0.106 g, 1.0 mmol) following typical procedure: 0.083 g (69% yield) of product was obtained after column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v); mp 83−85 °C (lit. 87−89 °C);[19] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.35−7.37 (m, 3H), 7.24−7.29 (m, 3H), 6.47−6.50 (m, 1H), 5.47 (s, 2H), 2.32−2.35 (m, 2H), 2.15−2.17 (m, 2H), 1.71−1.74 (m, 2H), 1.62−1.66 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 149.7, 134.8, 128.8, 128.4, 127.7, 127.1, 124.8, 118.2, 53.8, 26.2, 25.1, 22.3, 22.0; MS (+CI) m/z (%) 240.18 (M + H$^+$, 100).

4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)butan-1-ol (4j).[20] The compound was prepared from **2a** (0.067 g, 0.5 mmol) and **3j** (0.098 g, 1.0 mmol) following typical procedure: 0.097 g (84% yield) of product was obtained after column chromatography (eluent = petroleum ether/ethyl acetate 3:1 v/v); mp 77−79 °C (lit. 80 °C);[20] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.35−7.36 (m, 3H), 7.24−7.26 (m, 3H), 5.47 (s, 2H), 3.64 (t, J = 6.4 Hz, 2H), 2.84 (s, 1H), 2.71 (t, J = 7.6 Hz, 2H), 1.69−1.77 (m, 2H), 1.57−1.64 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 148.4, 134.7, 129.0, 128.6, 127.9, 120.7, 62.0, 53.9, 32.1, 25.4, 25.1; MS (+CI) m/z (%) 232.14 (M + H$^+$, 100).

4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)butanenitrile (4k).[21] The compound was prepared from **2a** (0.067 g, 0.5 mmol) and **3k** (0.093 g, 1.0 mmol) following typical procedure: 0.080 g (71% yield) of product was obtained after column chromatography (eluent = petroleum ether/ethyl acetate 4:1 v/v); mp 59−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.36−7.38 (m, 3H), 7.26−7.29 (m, 3H), 5.48 (s, 2H), 2.81 (t, J = 7.2 Hz, 2H), 2.38 (t, J = 7.2 Hz, 2H), 1.98−2.05 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 145.7, 134.5, 128.7, 128.3, 127.6, 121.0, 119.1, 53.6, 24.5, 23.9, 16.1; MS (+CI) m/z (%) 227.13 (M + H$^+$, 100).

1-Benzyl-4-cyclohexyl-1*H*-1,2,3-triazole (4l).[20] The compound was prepared from **2a** (0.067 g, 0.5 mmol) and **3l** (0.108 g, 1.0 mmol) following typical procedure: 0.074 g (61% yield) of product was obtained after column chromatography (eluent = petroleum ether/ethyl acetate 5:1 v/v); mp 109−111 °C (lit. 106 °C);[20] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.25−7.38 (m, 5H), 7.14 (s, 1H), 5.49 (s, 2H), 2.71−2.78 (m, 1H), 1.20−2.04 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 154.2, 135.0, 129.0, 128.6, 128.0, 119.2, 54.0, 35.3, 33.0, 26.1, 26.0; MS (ESI) m/z (%) 242.17 (M + H$^+$, 100).

1-(4-Methyl-benzyl)-4-phenyl-1*H*-1,2,3-triazole (4m).[21] The compound was prepared from **2b** (0.074 g, 0.5 mmol) and **3a** (0.102 g, 1.0 mmol) following typical procedure: 0.095 g (76% yield) of product was obtained after column chromatography (eluent = petroleum ether/ethyl acetate 3:1 v/v); mp 103−105 °C (lit. 105−106 °C);[21] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.76−7.79 (m, 2H), 7.63 (s, 1H), 7.39 (t, J = 3.6 Hz, 2H), 7.27−7.36 (m, 1H), 7.16−7.20 (m, 4H), 5.50 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 148.0, 138.6, 131.6, 130.5, 129.7, 128.7, 128.0, 125.6, 119.4, 53.9, 21.1; MS (ESI) m/z (%) 250.04 (M + H$^+$, 100).

dx.doi.org/10.1021/jo3008572 | J. Org. Chem. 2012, 77, 5844−5849

1-(4-Iodobenzyl)-4-phenyl-1*H*-1,2,3-triazole (4n).[22] The compound was prepared from **2c** (0.129 g, 0.5 mmol) and **3a** (0.102 g, 1.0 mmol) following typical procedure: 0.146 g (81% yield) of product was obtained after column chromatography (eluent = petroleum ether/ethyl acetate 3:1 v/v); mp 156−158 °C (lit. 154−156 °C);[22] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.80 (d, J = 1.6 Hz, 2H), 7.70−7.78 (m, 2H), 7.66 (s, 1H), 7.38−7.42 (m, 2H), 7.30−7.34 (m, 1H), 7.04 (d, J = 8.4 Hz, 2H), 5.50 (s, 2H);^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 148.4, 138.2, 134.3, 130.3, 129.8, 128.8, 128.2, 125.7, 119.4, 53.6; MS (ESI) m/z (%) 362.02 (M + H$^+$, 100).

1-(4-Methoxyphenethyl)-4-phenyl-1*H*-1,2,3-triazole (4o). The compound was prepared from **2d** (0.089 g, 0.5 mmol) and **3a** (0.102 g, 1.0 mmol) following typical procedure: 0.109 g (78% yield) of product was obtained as amorphous solid after column chromatography (eluent = petroleum ether/ethyl acetate 4:1 v/v); mp 134−136 °C;^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.77 (d, J = 7.3 Hz, 2H), 7.47 (s, 1H), 7.41 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.4 Hz, 1H), 7.04 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 4.60 (t, J = 7.2 Hz, 2H), 3.78 (s, 3H), 3.19 (t, J = 7.2 Hz, 2H);^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 158.7, 147.5, 130.7, 129.8, 129.0, 128.8, 128.1, 125.7, 120.0, 114.2, 65.9, 55.3, 52.0, 36.0, 29.7, 15.3; HRMS (ESI, TOF) calcd for $C_{17}H_{17}N_3O$ [M + H]$^+$ 280.1444, found 280.1440.

1-(*n*-Dodecyl)-4-(phenyl)-1*H*-1,2,3-triazole (4p).[18] The compound was prepared from **2e** (0.106 g, 0.5 mmol) and **3a** (0.102 g, 1.0 mmol) following typical procedure: 0.124 g (79% yield) of product was obtained after column chromatography (eluent = petroleum ether/ethyl acetate 10:1 v/v); mp 90−92 °C (lit. 90−92 °C);[18] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.84 (d, J = 1.3 Hz, 2H), 7.74 (s, 1H), 7.31−7.44 (m, 3H), 4.40 (t, J = 10.0 Hz, 2H), 1.91−1.97 (m, 2H), 1.26−1.35 (m, 18H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 147.7, 130.8, 128.8, 128.0, 125.7, 119.3, 50.5, 31.9, 30.4, 29.6, 29.5, 29.4, 29.3, 29.0, 26.5, 22.7, 14.1; MS (ESI) m/z (%) 314.26 (M + H$^+$, 100).

1-Cyclohexyl-4-phenyl-1*H*-1,2,3-triazole (4q).[23] The compound was prepared from **2f** (0.063 g, 0.5 mmol) and **3a** (0.102 g, 1.0 mmol) following typical procedure: 0.085 g (75% yield) of product was obtained after column chromatography (eluent = petroleum ether/ethyl acetate 6:1 v/v); mp 105−107 °C (lit. 106−110 °C);[23] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.82−7.84 (m, 2H), 7.78 (s, 1H), 7.41 (t, J = 7.2 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 4.43−4.51 (m, 1H), 2.23 (q, J_1 = 12.8 Hz, J_2 = 2.8 Hz, 2H), 1.90−1.95 (m, 2H), 1.73−1.83 (m, 3H), 1.41−1.51 (m, 2H), 1.26−1.33 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 147.2, 130.8, 128.7, 127.9, 125.5, 117.3, 60.0, 33.5, 25.1, 25.0; MS (+CI) m/z (%) 228.14 (M + H$^+$, 100).

4β-(4-Phenyl-1,2,3-triazole)-1-podophyllotoxin (4r).[24] The compound was prepared from **2g** (0.220 g, 0.5 mmol) and **3a** (0.102 g, 1.0 mmol) following typical procedure: 0.200 g (74% yield) of product was obtained after column chromatography (eluent = chloroform/ethyl acetate 2:1 v/v); mp 168−170 °C (lit. 155−157 °C);[24] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.78−7.81 (m, 2H), 7.33−7.44 (m, 4H), 6.68 (d, J = 4.4 Hz, 2H), 6.34 (s, 2H), 6.16 (d, J = 5.0 Hz, 1H), 6.01−6.04 (m, 2H), 4.80 (d, J = 5.0 Hz, 1H), 4.44−4.48 (m, 1H), 3.83 (s, 3H), 3.78(s, 6H), 3.37−3.42 (m, 1H), 3.22−3.31 (m, 1H), 3.10 (dd, J_1 = 5.0 Hz, J_2 = 14.3 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 173.1, 152.8, 149.5, 148.2, 148.0, 137.6, 134.2, 133.3, 129.8, 128.9, 128.6, 125.8, 124.7, 119.8, 110.6, 108.9, 108.2, 102.0, 67.5, 60.8, 58.7, 56.4, 43.7, 41.8, 37.2; MS (ESI) m/z (%) 542.19 (M + H$^+$, 100).

1-(4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)phenyl)ethanol (4s). To a mixture of azide (0.067 g, 0.5 mmol), alkyne (0.144 g, 1.0 mmol), 1,4-butanediol (0.361 g, 4 mmol), and toluene (0.5 mL) was added the catalyst $RuH_2(CO)(PPh_3)_3$ (23.4 mg, 0.025 mmol). The resulting solution was refluxed for 48 h. The solvent was evaporated under reduced pressure, and the residue was passed through flash column chromatography on silica gel (eluent = petroleum ether/ethyl acetate 2:1 v/v) to afford the desired product as pale yellow amorphous solid: 64 mg (46% yield); mp 108−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.78 (d, J = 7.7 Hz, 2H), 7.65 (s, 1H), 7.30−7.42 (m, 7H), 5.58 (s, 2H), 4.92 (q, J_1 = 6.2 Hz, J_2 = 12.6 Hz, 1H), 1.90 (s, 1H), 6.44 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C) δ 148.0, 146.0, 134.7, 129.6, 129.2, 128.8, 128.1, 125.9, 125.8, 119.5, 70.0, 54.2, 25.2; HRMS (EI, TOF) calcd for $C_{17}H_{17}N_3O$ [M]$^+$ 279.1366, found 279.1373.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H spectra for products **4a−s**, ^{13}C NMR spectra for new compounds **4f**, **4g**, **4o**, and **4s**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Hong Kong Research Grant Council (Projects No. HKUST 601709, HKUST 601408, and HKU1/CRF/08), the National Natural Science Foundation of China (Projects No. 21172069, 21190033, and 20902020), the Innovation Program of Shanghai Municipal Education Commission (Project No. 12ZZ050), and the Fundamental Research Funds for the Central Universities.

■ REFERENCES

(1) (a) Lwowski, W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. *1*, pp 559. (b) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2002.

(2) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 565.

(3) Reactions involving activated alkynes or strained alkynes can be accomplished under relatively mild conditions. See: Jewett, J. C.; Bertozzi, C. R. *Chem. Soc. Rev.* **2010**, *39*, 1272.

(4) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210.

(5) (a) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

(6) (a) Theme issue on Click chemistry: *Chem. Soc. Rev.* **2010**, (4), 39. For additional reviews, see: (b) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952. (c) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249 and the references therein. (d) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278. (e) Lutz, J.-F.; Zarafshani, Z. *Adv. Drug Delivery Rev.* **2008**, *60*, 958. (f) Fokin, V. V. *ACS Chem. Biol.* **2007**, *2*, 775. (g) Johnson, J. A.; Koberstein, J. T.; Finn, M. G.; Turro, N. J. *Macromol. Rapid Commun.* **2008**, *29*, 1052. (h) Wu, P.; Fokin, V. V. *Aldrichimica Acta* **2007**, *40*, 7.

(7) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302.

(8) (a) Zn/C catalyzed reactions: Meng, X.; Xu, X.; Gao, T.; Chen, B. *Eur. J. Org. Chem.* **2010**, 5409. (b) NMe_4OH catalyzed reactions: Kwok, S. W.; Fosing, J. R.; Fraser, R.; Rodionov, V. O.; Fokin, V. V. *Org. Lett.* **2010**, *12*, 4217.

(9) (a) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998. (b) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923. (c) Boren, B. C.; Fokin, V. V. *Org. Lett.* **2007**, *9*, 5337. (d) Oppilliart, S.; Mousseau, G.; Zhang, L.; Jia, G.; Thuéry, P.; Rousseau, B.; Cintrat, J. C. *Tetrahedron* **2007**, *63*, 8094.

(10) Other studies on RuAAC: (a) Hou, D. R.; Kuan, T. C.; Li, Y. K.; Lee, R.; Huang, K. W. *Tetrahedron Lett.* **2010**, *66*, 9415. (b) Yap, A. H.; Weinreb, S. M. *Tetrahedron Lett.* **2006**, *47*, 3035. (c) Majireck, M.

M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680. (d) Johansson, J. R.; Lincoln, P.; Norden, B.; Kann, N. *J. Org. Chem.* **2011**, *76*, 2355.
(11) For recent applications of RuAAC, see: (a) Empting, M.; Avrutina, O.; Meusinger, R.; Fabritz, S.; Reinwarth, M.; Biesalski, M.; Voigt, S.; Buntkowsky, G.; Kolmar, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 5207. (b) Chardon, E.; Puleo, G. L.; Dahm, G.; Guihard, G.; Bellemin,-Laponnaz, S. *Chem. Commun.* **2011**, *47*, 5864. (c) Isidro,-Llobet, A.; Murillo, T.; Bello, P.; Cilibrizzi, A.; Hodgkinson, J. T.; Galloway, W. R. J. D.; Bender, A.; Welch, M.; Spring, D. R. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 6793. (d) Poecke, S. V.; Negri, A.; Gago, F.; Daele, I. V.; Solaroli, N.; Karlsson, A.; Balzarini, J.; Calenbergh, S. V. *J. Med. Chem.* **2010**, *53*, 2902. (e) Krause, M. R.; Goddard, R.; Kubik, S. *Chem. Commun.* **2010**, *46*, 5307. (f) Horne, W. S.; Olsen, C. A.; Beierle, J. M.; Montero, A.; Ghadiri, M. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 4718. (g) Chemama, M.; Fonvielle, M.; Arthur, M.; Valery, J. M.; Etheve-Quelquejeu, M. *Chem.—Eur. J.* **2009**, *15*, 1929. (h) Kelly, A. W.; Wei, J.; Kesavan, K.; Marie, J.-C.; Windmon, N.; Young, D. W.; Maucaurelle, L. A. *Org. Lett.* **2009**, *11*, 2257.
(12) (a) Yousefzadi, M.; Sharifi, M.; Behmanesh, M.; Moyano, E.; Bonfill, M.; Cusido, R. M.; Palazon, J. *Eng. Life Sci.* **2010**, *10*, 281. (b) Garcia, E. S.; Azambuja, P. *Toxicon* **2004**, *44*, 431.
(13) Asano, K.; Matsubara, S. *Org. Lett.* **2010**, *12*, 4988.
(14) Zhou, X.-M.; Wang, Z.-Q.; Chang, J.-Y.; Chen, H.-X.; Cheng, Y.-C.; Lee, K.-H. *J. Med. Chem.* **1991**, *34*, 3346.
(15) (a) Dash, B. P.; Satapathy, R.; Gaillard, E. R.; Norton, K. M.; Maguire, J. A.; Chug, N.; Hosmane, N. S. *Inorg. Chem.* **2011**, *50*, 5485. (b) López-Pérez, J. L.; Olmo, E.; Pascual-Teresa, B.; Abad, A.; Feliciano, A. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1283.
(16) Ahmad, N.; Levison, J. J.; Robinson, S. D.; Uttley, M. F.; Wonchoba, E. R.; Parshall, G. W. *Inorg. Synth.* **1974**, *15*, 45.
(17) Lőrincz, K.; Kele, P.; Novák, Z. *Synthesis* **2009**, 3527.
(18) Wang, D.; Li, N.; Zhao, M.; Shi, W.; Ma, C.; Chen, B. *Green Chem.* **2010**, *12*, 2120.
(19) Zhou, Y.; Lecourt, T.; Micouin, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2607.
(20) Chassaing, S.; Sido, A. S. S.; Alix, A.; Kumarraja, M.; Pale, P.; Sommer, J. *Chem.—Eur. J.* **2008**, *14*, 6713.
(21) González, J.; Pérez, V. M.; Jiménez, D. O.; Lopez-Valdez, G.; Corona, D.; Cuevas-Yañez, E. *Tetrahedron Lett.* **2011**, 3514.
(22) Gonda, Z.; Novák, Z. *Dalton Trans.* **2010**, *39*, 726.
(23) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *Eur. J. Org. Chem.* **2010**, 1875.
(24) Shi, J. F.; Wang, Y. G. *Chin. J. Org. Chem.* **2003**, *11*, 1244.

dx.doi.org/10.1021/jo3008572 | *J. Org. Chem.* 2012, 77, 5844−5849