An Efficient Copper-Catalyzed Three-Component Synthesis of 3-C-Linked Glycosyl Iminocoumarins

Kalanidhi Palanichamy, Sankar R. Suravarapu, Krishna P. Kaliappan*

Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400 076, India
Fax +91(22)25723480; E-mail: kpk@chem.iitb.ac.in

Received: 03.04.2012; Accepted: 10.04.2012

Abstract: An efficient general strategy was developed for the synthesis of previously unknown 3-C-linked glycosyl iminocoumarins. The strategy involves a copper-catalyzed multicomponent reaction of sugar-derived alkynes with tosyl azide and salicylaldehyde to give a diverse array of glycosyl iminocoumarins in good yields. These compounds can serve as appropriate precursors for the synthesis of the corresponding coumarin 3-C-glycosides.

Key words: multicomponent reactions, copper, alkynes, azides, glycosides, glycosylations, heterocycles

The *C*-aryl glycosides[1] are a group of compounds that includes many natural products such as ravidomycin (**1**)[2] and gilvocarcin M (**2**)[3] (Figure 1). Because the aromatic ring is directly attached to the sugar unit at an anomeric center through a C–C bond, *C*-aryl glycosides show greater stability to enzymatic or acidic hydrolysis than do O- or N-glycosides.[4] Glycosides in which the sugar unit is linked to a coumarin[5] pharmacophore constitute a novel class of glycosides, namely the coumarin glycosides. In accord with the intriguing biological profile of coumarins, coumarin glycosides exhibit a broad spectrum of biological activities, such as anti-inflammatory,[6] anticoagulant,[7] anticancer,[8] and antibacterial activities,[9] and they are also useful as fluorescent probes for studies on ultrafast DNA dynamics.[10]

Although there are many naturally occurring *O*-glycosyl coumarins[11] [e.g., dauroside A (**3**),[12]], the only coumarin *C*-glycoside that has been found in nature is dauroside D (**4**),[13] also known as mulberroside B,[14] which exhibits spasmolytic and hypotensive activities.

Whereas iminocoumarins have been shown to be inhibitors of protein tyrosine kinase in cancer research,[15] the chemistry of glycosyl iminocoumarins, to the best of our knowledge, remains unexplored. We therefore hypothesized that linking of an iminocoumarin scaffold to a carbohydrate unit might lead to a new class of glycosides that might have interesting biological profiles.

In view of the biological and other applications of coumarin and iminocoumarin derivatives, many methods have been developed for the synthesis of these compounds. However, most of these methods have severe shortcomings, such as a lack of generality or a lack of tolerance to sensitive functional groups. Consequently, the development of new and mild methods for constructing coumarin and iminocoumarin frameworks is an attractive goal. Since the first syntheses of coumarin C-glycosides by Mahling and Schmidt,[16] many reports have appeared on the synthesis of *C*-glycosyl coumarin derivatives in which the aromatic ring of the coumarin unit is attached to the anomeric carbon of the sugar.[4j,17] However, there are few reports on the synthesis of coumarin 3- or 4-*C*-glycosides. Dhavale and co-workers reported a Knoevenagel reaction/lactonization-based approach to the synthesis of *C*-glycosyl coumarins in which the coumarin ring is linked to the C-5 carbon of the pyranose moiety with a free anomeric center (Scheme 1).[18] Later, Roy and co-workers developed a one-pot Heck reaction and lactonization methodology for the synthesis of 3- and 4-C-linked mannopyranosyl coumarins (Scheme 1).[19]

Multicomponent reactions have become attractive tools, particularly in combinatorial organic synthesis, as they permit the construction of complex structures through the

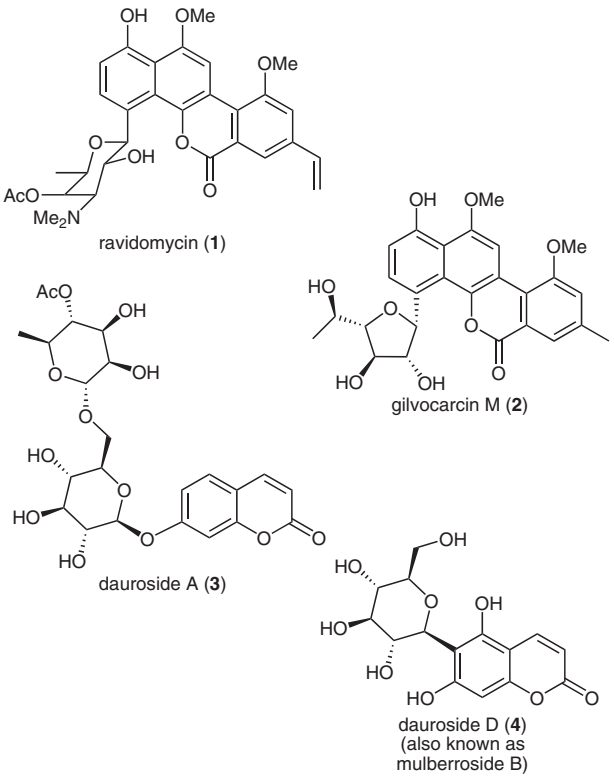
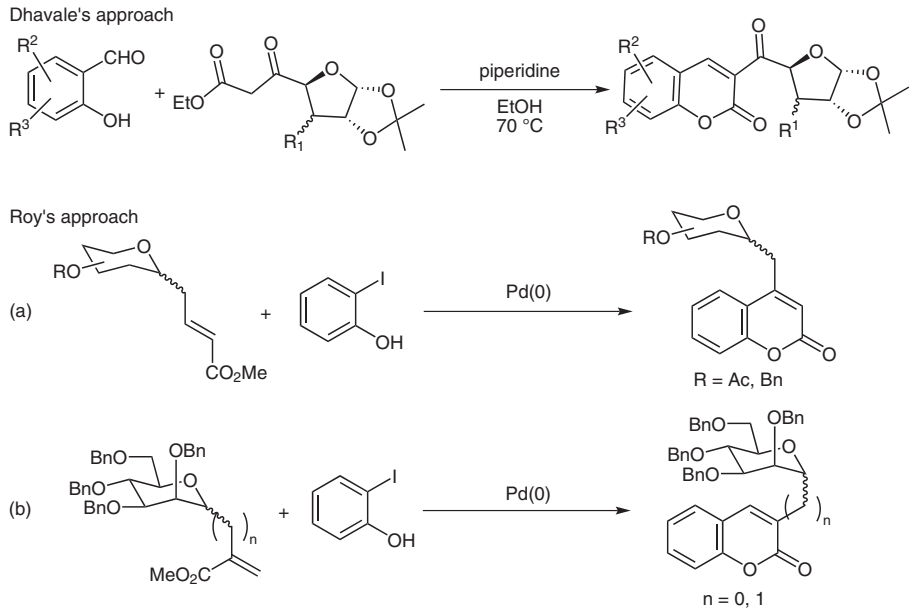


Figure 1 Examples of *C*-aryl glycosides (ravidomycin and gilvocarcin M), a coumarin O-glycoside (dauroside A), and a coumarin C-glycoside (dauroside D)

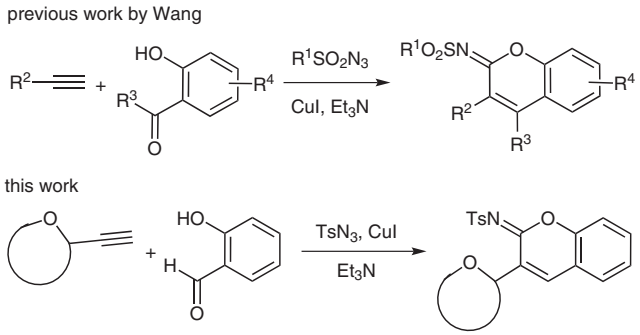
SYNTHESIS 2012, 44, 1841–1848
Advanced online publication: 10.05.2012
DOI: 10.1055/s-0031-1289763; Art ID: SS-2012-C0331-ST



Scheme 1 Previous approaches to coumarin 3- and 4-C-linked glycosides

formation of multiple covalent bonds in a one-pot process.[20] Several years ago, Chang and co-workers reported a copper-catalyzed multicomponent reaction of alkynes and sulfonyl azides with amines, water, or alcohols to give *N*-sulfonylamidines, amides, and *N*-sulfonylimidates, respectively.[21] This methodology has been further developed[22] by Chang,[23] Wang,[24] and others[25] to construct a diverse array of interesting compounds. The technique was used by Wang to synthesize iminocoumarins through a copper-catalyzed multicomponent reaction of alkynes, sulfonyl azides, and 2-hydroxybenzaldehydes or 2-hydroxyacetophenones (Scheme 2).[24a]

In continuation of our interest in exploring the application of sugar-derived alkynes,[26] it occurred to us that copper-catalyzed multicomponent reaction of sugar-derived alkynes with tosyl azide and 2-hydroxybenzaldehyde should provide *C*-glycosyl iminocoumarins that might serve as precursors of coumarin 3-C-glycosides. Here, we report our efforts to synthesize several 3-C-linked glycosyl iminocoumarins.



Scheme 2 Wang's multicomponent approach to the synthesis of iminocoumarins, and our approach to glycosyl iminocoumarins

To test our hypothesis, we chose a suite of sugar-derived alkynes (Figure 2), which we prepared by the procedures described in the literature.[26,27] Having prepared these alkynes, we initially examined the copper-catalyzed multicomponent reaction of alkyne **5** (1 mmol) with tosyl azide (1 mmol) and salicylaldehyde **13** (1 mmol) in the presence of copper(I) iodide (0.1 mmol) and triethylamine (2 mmol) in dichloromethane at room temperature (Table 1, entry 1). The reaction was sluggish and was incomplete even after 30 hours, giving the required product **14** in only a 36% yield. To optimize the reaction, we screened several conditions with various solvents and bases (Table 1). Whereas 1,4-dioxane (entry 2) or toluene (entry 3) gave the desired product **14** in 43% and 51% yield, respectively, **14** was obtained in 60% yield when the reaction was carried out in acetonitrile (entry 4). When the reaction was performed in tetrahydrofuran (entry 5) for 24 hours, it went nearly to completion, giving the desired glycosyl iminocoumarin **14** in 79% yield. When triethylamine was replaced with pyridine (entry 6) in tetrahydrofuran, the yield of compound **14** was poor (22%). Furthermore, no reaction was observed in the presence of 4-(*N*,*N*-dimethylamino)pyridine (entry 7) or potassium carbonate (entry 8). However, the required glycosyl iminocoumarin was obtained in a moderate yield (57%) when the reaction was performed in the presence of *N*,*N*-diisopropylethylamine (entry 9). We therefore concluded that triethylamine as the base and tetrahydrofuran as the solvent provide the optimal conditions for this reaction.

Next, we examined the scope of the reaction with various sugar-derived alkyne templates under our optimized conditions (Table 2). In all the cases, the multicomponent reaction occurred smoothly to give the corresponding 3-*C*-glycosyl iminocoumarin in 51–91% yield. In the case of the sterically hindered alkynes **10** and **11** (entries 6 and 7,

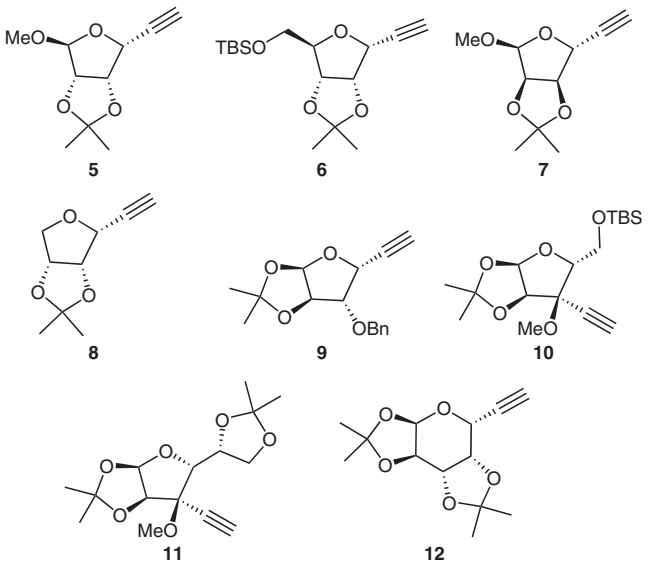
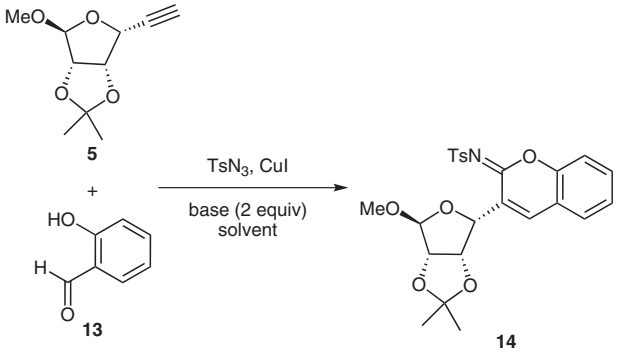


Figure 2 Selected sugar-derived alkynes for the multicomponent reaction

Table 1 Screening of Bases and Solvents To Optimize the Reaction Conditions

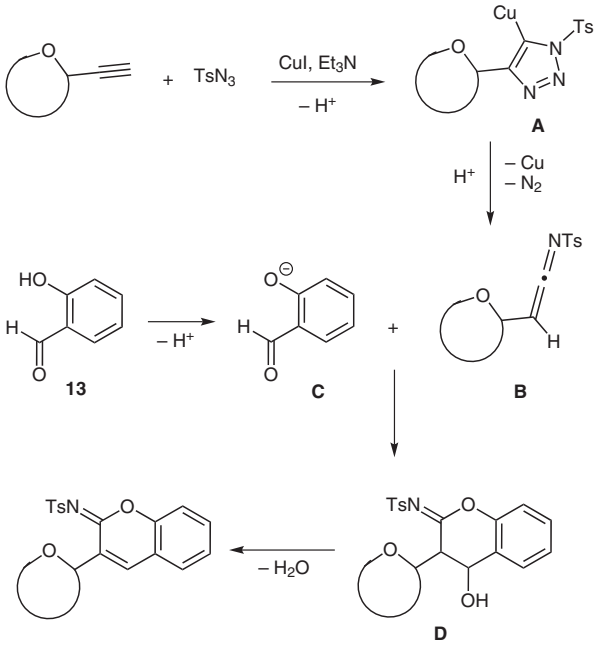


Entry[a]	Base	Solvent	Time (h)	Yield (%)
1	Et_3N	CH_2Cl_2	30	36
2	Et_3N	1,4-dioxane	24	43
3	Et_3N	toluene	24	51
4	Et_3N	MeCN	24	60
5	Et_3N	THF	24	79
6	py	THF	30	22
7	DMAP	THF	24	–
8	DIPEA	THF	24	57
9	K_2CO_3	THF	24	–

[a] The reaction was carried out with alkyne **5** (1 mmol), TsN_3 (1 mmol), and salicylaldehyde (1 mmol) in the presence of CuI (0.1 mmol) and base (2 mmol) in the appropriate solvent (5 mL) at r.t.

respectively), the reaction gave the corresponding products **19** and **20** in moderate yields.

As originally proposed by Chang[21] and as postulated by Wang,[24a] the reaction proceeds by a stepwise mechanism, as outlined in Scheme 3. In the presence of copper(I) iodide and triethylamine, the sugar-derived terminal alkyne and tosyl azide react to give the triazolyl copper species **A**, which eliminates dinitrogen to give the reactive ketenimine **B**. This undergoes addition with the phenolate **C**, derived from salicylaldehyde **13**. Subsequent intramolecular cyclization leads to intermediate **D**, which is finally dehydrated to give the required glycosyl iminocoumarin.

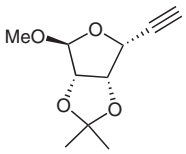
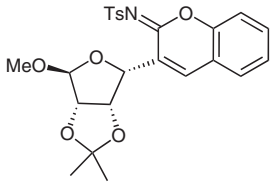
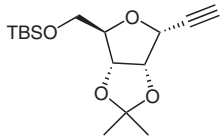
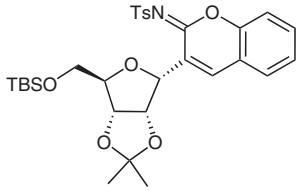
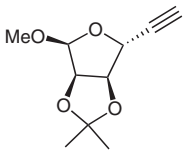
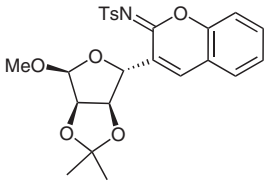
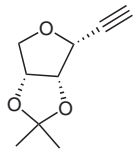
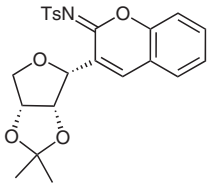
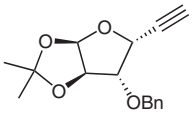
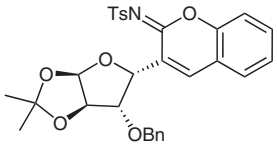
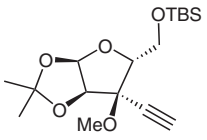
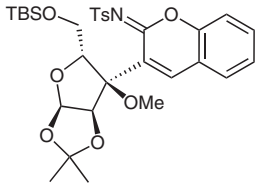
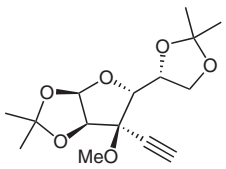
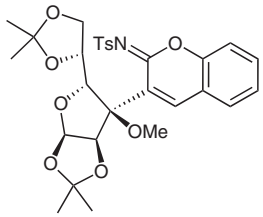
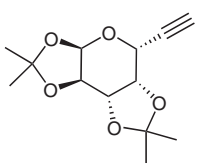
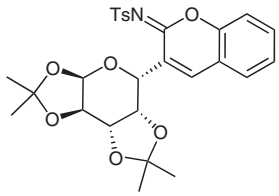


Scheme 3 Postulated mechanism for the multicomponent reaction

In summary, we have reported for the first time the synthesis of a variety of 3-*C*-glycosyl iminocoumarins in which the carbohydrate unit is directly attached to the C-3 carbon of the iminocoumarin skeleton. The synthesis involves a copper-catalyzed multicomponent reaction of a sugar-derived alkyne, tosyl azide, and salicylaldehyde to form the iminocoumarin framework. The resulting glycosyl iminocoumarins can serve as intermediates for the synthesis of the corresponding coumarin 3-C-glycosides. Our strategy therefore opens a path to the synthesis of a series of 3-C-linked glycosyl iminocoumarins and coumarins that might have interesting biological profiles.

Unless and otherwise noted, all starting materials and reagents were obtained from commercial suppliers and used after further purification. THF was distilled from sodium–benzophenone ketyl and toluene was distilled from Na. CH_2Cl_2, DMF, hexanes, and pyridine were all freshly distilled from CaH_2. All solvents for routine isolation of products and chromatography were of reagent grade and glass distilled. Reaction flasks were dried in an oven at 100 °C for 12 h. Air- and moisture-sensitive reactions were performed under an argon/UHP N_2 atmosphere. Chromatography was performed by using silica gel (100–200 mesh; Acme) with the indicated solvents. All reactions were monitored by TLC on 0.25-mm E. Merck silica plates (60F-254) visualized with UV radiation, with a charring soln [prepared by dropwise addition of concd H_2SO_4 (5 mL) to a soln of

Table 2 Copper-Catalyzed Multicomponent Reaction of Various Sugar-Derived Alkynes and Tosyl Azide with Salicylaldehyde

Entry[a]	Alkyne	Product	Yield (%)
1	**5** 	**14** 	79
2	**6** 	**15** 	75
3	**7** 	**16** 	83
4	**8** 	**17** 	74
5	**9** 	**18** 	91
6	**10** 	**19** 	56
7	**11** 	**20** 	51
8	**12** 	**21** 	68

[a] Reaction conditions: Alkyne (1 mmol), TsN_3 (1 mmol), salicylaldehyde (1 mmol), CuI (0.1 mmol), and Et_3N (2 mmol) in THF (5 mL) at r.t. for 24 h.

phosphomolybdic acid (1 g) and $Ce(SO_4)_2$ (2 g) in H_2O (95 mL)], or with alkaline $KMnO_4$ [prepared by dissolving $KMnO_4$ (2 g) and $NaHCO_3$ (4 g) in H_2O (100 mL)] with heat as a developing agent. Optical rotations were recorded on Autopol IV automatic polarimeter. IR spectra were recorded on Thermo Nicolet Avater 320 FT-IR and Nicolet Impact 400 spectrometers. Mass spectra were recorded on a Waters Micromass-Q-Tof micro™ (YA105) spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400-MHz spectrometer and were processed by using MestReNova software.

Copper-Catalyzed Multicomponent Reaction; General Procedure

Et_3N (2 mmol) was added dropwise to a suspension of TsN_3 (1 mmol), the appropriate carbohydrate-derived alkyne (1 mmol), CuI (0.1 mmol), and salicylaldehyde (1 mmol) in THF (5 mL) at r.t., and the mixture was stirred at r.t. for 24 h under N_2. The resulting mixture was concentrated and the residue was diluted with CH_2Cl_2 (20 mL) and washed successively with H_2O (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated. The resulting crude product was purified by column chromatography (silica gel, hexanes–EtOAc) to give the corresponding glycosyl iminocoumarin.

***N*-{3-[(3a*S*,4*R*,6*S*,6a*S*)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]-2*H*-chromen-2-ylidene}-4-tolylsulfonamide (14)**

By following the general procedure, the multicomponent reaction of alkyne **5** (30 mg, 0.15 mmol) gave a white solid; yield: 56 mg (79%); mp 146–148 °C; R_f = 0.61 (EtOAc–hexanes, 1:1); $[\alpha]_D^{20}$ –19.3 (*c* 0.9, $CHCl_3$).

IR (KBr): 3020, 2933, 1635, 1561, 1375, 1216, 1158, 1086, 1028, 968, 909 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.3 Hz, 2 H), 7.87 (s, 1 H), 7.56–7.52 (m, 2 H), 7.41 (d, *J* = 8.2 Hz, 1 H), 7.36–7.27 (m, 3 H), 5.07–5.02 (m, 3 H), 4.61 (d, *J* = 5.3 Hz, 1 H), 3.34 (s, 3 H), 2.41 (s, 3 H), 1.29 (s, 3 H), 1.24 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3, 152.3, 143.4, 139.0, 131.9, 129.9, 129.4, 128.4, 127.6, 125.9, 125.6, 119.5, 116.7, 112.7, 107.0, 84.9, 79.7, 55.0, 26.2, 24.9, 21.8.

HRMS (ESI): *m/z* calcd for $C_{24}H_{25}NO_7S$: 472.1430; found: 472.1433.

***N*-{3-[(3a*S*,4*R*,6*R*,6a*R*)-6-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]-2*H*-chromen-2-ylidene}-4-tolylsulfonamide (15)**

By following the general procedure, the multicomponent reaction of alkyne **6** (30 mg, 0.096 mmol) gave a low-melting solid; yield: 42 mg (75%); R_f = 0.74 (EtOAc–hexanes, 1:1); $[\alpha]_D^{20}$ –27.8 (*c* 0.54, $CHCl_3$).

IR ($CHCl_3$): 2929, 2857, 2102, 1636, 1564, 1457, 1381, 1324, 1259, 1216, 1161, 1088, 911, 838, 761, 671, 609 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.2 Hz, 2 H), 7.87 (s, 1 H), 7.54–7.49 (m, 2 H), 7.43 (d, *J* = 8.1 Hz, 1 H), 7.34–7.21 (m, 3 H), 5.17 (d, *J* = 3.4 Hz, 1 H), 5.04 (dd, *J* = 5.9, 3.4 Hz, 1 H), 4.83 (d, *J* = 5.9 Hz, 1 H), 4.25 (t, *J* = 3.4 Hz, 1 H), 3.78 (dd, *J* = 10.9, 3.5 Hz, 1 H), 3.73 (dd, *J* = 10.9, 3.5 Hz, 1 H), 2.41 (s, 3 H), 1.28 (s, 3 H), 1.27 (s, 3 H), 0.84 (s, 9 H), 0.00 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 152.3, 143.2, 139.5, 138.2, 131.6, 129.4, 128.3, 127.5, 127.2, 125.8, 119.6, 116.7, 112.4, 84.6, 83.2, 81.7, 79.7, 65.1, 26.4, 26.0, 25.0, 21.7, 18.3, –5.4, –5.5.

HRMS (ESI): *m/z* calcd for $C_{30}H_{39}NO_7SSi$: 586.2295; found: 586.2311.

***N*-{3-[(3a*R*,4*R*,6*S*,6a*R*)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]-2*H*-chromen-2-ylidene}-4-tolylsulfonamide (16)**

By following the general procedure, the multicomponent reaction of alkyne **7** (50 mg, 0.25 mmol) gave a white solid; yield: 98 mg (83%); mp 99–101 °C; R_f = 0.51 (EtOAc–hexanes, 1:1); $[\alpha]_D^{20}$ –37.0 (*c* 0.9, $CHCl_3$).

IR (KBr): 3855, 3741, 3020, 2930, 1636, 1569, 1458, 1375, 1303, 1216, 1158, 1086, 837 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.3 Hz, 2 H), 7.89 (d, *J* = 0.7 Hz, 1 H), 7.57 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.52–7.49 (m, 2 H), 7.35 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 5.3 (s, 1 H), 5.15 (s, 1 H), 4.85 (dd, *J* = 6.0, 1.6 Hz, 1 H), 4.52 (d, *J* = 6.0 Hz, 1 H), 3.45 (s, 3 H), 2.42 (s, 3 H), 1.53 (s, 3 H), 1.31 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 152.4, 143.1, 139.6, 138.4, 132.2, 129.2, 128.6, 128.6, 127.3, 125.9, 119.2, 116.9, 112.9, 112.2, 85.2, 85.1, 84.4, 56.5, 26.9, 25.3, 21.7.

HRMS (ESI): *m/z* calcd for $C_{24}H_{25}NO_7S$: 472.1430; found: 472.1425.

***N*-{3-[(3a*S*,4*R*,6a*R*)-2,2-Dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]-2*H*-chromen-2-ylidene}-4-tolylsulfonamide (17)**

By following the general procedure, the multicomponent reaction of alkyne **8** (20 mg, 0.12 mmol) gave a white solid; yield: 39 mg (74%); mp 136–137 °C; R_f = 0.45 (EtOAc–hexanes, 1:1); $[\alpha]_D^{20}$ –53.3 (*c* 0.8, $CHCl_3$).

IR (KBr): 2926, 2853, 2252, 2102, 1635, 1560, 1458, 1380, 1320, 1261, 1216, 1159, 1088, 913, 815, 736, 672, 611 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.2 Hz, 2 H), 7.87 (s, 1 H), 7.55–7.50 (m, 2 H), 7.39–7.33 (m, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 5.04 (dd, *J* = 6.0, 3.6 Hz, 1 H), 4.83 (dd, *J* = 6.0, 3.6 Hz, 1 H), 4.62 (d, *J* = 3.6 Hz, 1 H), 4.14 (d, *J* = 10.7 Hz, 1 H), 3.62 (dd, *J* = 10.7, 3.6 Hz, 1 H), 2.41 (s, 3 H), 1.32 (s, 3 H), 1.26 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4, 152.3, 143.5, 139.2, 139.1, 131.9, 129.4, 128.4, 127.7, 126.0, 125.6, 119.5, 116.6, 112.3, 81.1, 80.3, 79.2, 72.7, 26.1, 24.8, 21.7.

HRMS (ESI): *m/z* calcd for $C_{23}H_{23}NO_6S$: 442.1324; found: 442.1329.

***N*-{3-[(3a*R*,5*R*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-2*H*-chromen-2-ylidene}-4-tolylsulfonamide (18)**

By following the general procedure, the multicomponent reaction of alkyne **9** (50 mg, 0.18 mmol) gave a white solid; yield: 91 mg (91%); mp 108–109 °C; R_f = 0.63 (EtOAc–hexanes, 1:1); $[\alpha]_D^{20}$ –74.8 (*c* 0.9, $CHCl_3$).

IR (KBr): 3020, 2928, 1629, 1564, 1216, 1159, 1086, 1020, 909 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97–7.95 (m, 3 H), 7.55 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.48 (dd, *J* = 7.5, 1.4 Hz, 1 H), 7.43 (d, *J* = 7.5 Hz, 1 H), 7.33 (td, *J* = 7.5, 1.4 Hz, 1 H), 7.25 (d, *J* = 7.5 Hz, 2 H), 7.12 (m, 3 H), 6.95 (m, 2 H), 6.03 (d, *J* = 3.7 Hz, 1 H), 5.27 (dd, *J* = 3.3, 1.4 Hz, 1 H), 4.60 (d, *J* = 3.7 Hz, 1 H), 4.53 (d, *J* = 3.3 Hz, 1 H), 4.44, 4.32 (ABq, J_{AB} = 11.6 Hz, 2 H), 2.36 (s, 3 H), 1.53 (s, 3 H), 1.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 152.3, 143.5, 139.4, 139.2, 137.3, 131.9, 129.5, 128.5, 128.5, 127.9, 127.6, 127.6, 126.0, 125.6, 119.4, 116.5, 112.6, 104.8, 83.4, 82.5, 78.2, 73.3, 27.3, 26.6, 21.7.

HRMS (ESI): *m/z* calcd for $C_{30}H_{29}NO_7S$: 548.1743; found: 548.1739.

***N*-{3-[(3a*R*,5*R*,6*R*,6a*R*)-5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-6-methoxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl]-2*H*-chromen-2-ylidene}-4-tolylsulfonamide (19)**

By following the general procedure, the multicomponent reaction of alkyne **10** (50 mg, 0.15 mmol) gave a low-melting solid; yield: 50 mg (56%); R_f = 0.70 (EtOAc–hexanes, 1:1); $[\alpha]_D^{20}$ –110.9 (*c* 0.61, $CHCl_3$).

IR ($CHCl_3$): 2929, 1628, 1574, 1455, 1375, 1321, 1259, 1216, 1159, 1089, 1019, 911, 838, 759, 671, 623 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 1 H), 7.94 (d, *J* = 8.2 Hz, 2 H), 7.58 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.52 (dd, *J* = 7.7, 1.3 Hz, 1 H), 7.46 (d, *J* = 7.7 Hz, 1 H), 7.35 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 5.71 (d, *J* = 3.9 Hz, 1 H), 5.27 (d, *J* = 3.9 Hz, 1 H), 4.17 (t, *J* = 4.9 Hz, 1 H), 3.56 (dd, *J* = 11.6, 4.9 Hz, 1 H), 3.43 (dd, *J* = 11.6, 4.9 Hz, 1 H), 3.30 (s, 3 H), 2.41 (s, 3 H), 1.56 (s, 3 H), 1.24 (s, 3 H), 0.71 (s, 9 H), –0.12 (s, 3 H), –0.19 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 152.4, 143.6, 142.8, 139.1, 132.7, 129.6, 128.6, 127.3, 126.0, 125.7, 119.2, 116.5, 111.8, 106.5, 87.8, 83.8, 81.4, 61.6, 53.9, 26.8, 26.5, 25.9, 21.8, 18.4, –5.4, –5.4.

HRMS (ESI): *m/z* calcd for $C_{31}H_{41}NO_8SSi$: 616.2400; found: 616.2405.

***N*-(3-{(3a*R*,5*R*,6*R*,6a*R*)-5-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-methoxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl}-2*H*-chromen-2-ylidene)-4-tolylsulfonamide (20)**

By following the general procedure, the multicomponent reaction of alkyne **11** (50 mg, 0.17 mmol) gave a low-melting solid; yield: 49 mg (51%); R_f = 0.53 (EtOAc–hexanes, 1:1); $[\alpha]_D^{20}$ –97.4 (*c* 0.32, $CHCl_3$).

IR ($CHCl_3$): 3366, 2926, 2854, 2104, 1561, 1455, 1216, 1160, 1089, 1018, 911, 853, 760, 669 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 7.93 (d, *J* = 8.3 Hz, 2 H), 7.61 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.57 (dd, *J* = 7.7, 1.3 Hz, 1 H), 7.49 (d, *J* = 7.7 Hz, 1 H), 7.37 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.32 (d, *J* = 8.3 Hz, 2 H), 5.63 (d, *J* = 3.8 Hz, 1 H), 5.32 (d, *J* = 3.8 Hz, 1 H), 4.06 (d, *J* = 8.4 Hz, 1 H), 3.82 (dd, *J* = 8.3, 6.8 Hz, 1 H), 3.72 (dd, *J* = 8.3, 6.8 Hz, 1 H), 3.49 (dt, *J* = 8.4, 6.8 Hz, 1 H), 3.30 (s, 3 H), 2.41 (s, 3 H), 1.56 (s, 3 H), 1.39 (s, 3 H), 1.21 (s, 3 H), 1.10 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 152.5, 145.2, 143.8, 139.0, 133.1, 129.9, 128.8, 127.3, 126.7, 126.1, 119.1, 116.6, 111.8, 109.6, 106.8, 89.0, 84.0, 81.1, 74.1, 68.1, 53.9, 26.8, 26.8, 26.3, 25.8, 21.8.

HRMS (ESI): *m/z* calcd for $C_{29}H_{33}NO_9S$: 572.1954; found: 572.1971.

***N*-{3-[(3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-Tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4',5'-*d*]pyran-5-yl]-2*H*-chromen-2-ylidene}-4-tolylsulfonamide (21)**

By following the general procedure, the multicomponent reaction of alkyne **12** (30 mg, 0.12 mmol) gave a white solid; yield: 42 mg (68%); mp 92–93 °C; R_f = 0.60 (EtOAc–hexanes, 1:1); $[\alpha]_D^{20}$ –9.5 (*c* 0.8, $CHCl_3$).

IR (KBr): 3020, 2990, 2926, 1633, 1560, 1457, 1383, 1318, 1255, 1214, 1160, 1086, 1070, 1002, 905 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.2 Hz, 2 H), 7.84 (s, 1 H), 7.54–7.51 (m, 2 H), 7.40 (d, *J* = 8.2 Hz, 1 H), 7.34–7.28 (m, 3 H), 5.66 (d, *J* = 5.0 Hz, 1 H), 5.01 (s, 1 H), 4.71 (dd, *J* = 7.8, 2.2 Hz, 1 H), 4.64 (dd, *J* = 7.8, 2.2 Hz, 1 H), 4.40 (dd, *J* = 5.0, 2.2 Hz, 1 H), 2.41 (s, 3 H), 1.51 (s, 3 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.27 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 152.3, 143.3, 140.1, 139.3, 131.9, 129.6, 129.4, 128.6, 127.5, 126.2, 125.9, 119.7, 116.6, 109.4, 97.0, 71.1, 70.9, 70.8, 65.0, 26.2, 26.1, 25.2, 24.4, 21.7.

HRMS (ESI): *m/z* calcd for $C_{27}H_{29}NO_8S$: 528.1692; found: 528.1689.

Acknowledgment

K.P.K. thanks the DST for the award of the Swarnajayanti fellowship. K.P. thanks CSIR, New Delhi, for a fellowship.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) For general reviews on glycosides, see: (a) Watanabe, K. A. In *The Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press: New York, **1994**, 421. (b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Elsevier: Oxford, **1995**. (c) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, **1995**. (d) Shaban, M. A. E.; Nasr, A. Z. *Adv. Heterocycl. Chem.* **1997**, *68*, 223. (e) Shaban, M. A. E. *Adv. Heterocycl. Chem.* **1997**, *70*, 163. (f) Beau, J. M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1. (g) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55. (h) Krohn, K.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 127. (i) Du, Y. G.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913. (j) Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4395. (k) Somsák, L. *Chem. Rev.* **2001**, *101*, 81. (l) Liu, L.; McKee, M.; Postema, M. H. D. *Curr. Org. Chem.* **2001**, *5*, 1133. (m) Meo, P.; Osborn, H. M. I. In *Carbohydrates*; Osborn, H. M. I., Ed.; Academic Press: New York, **2003**, Chap. 10 337. (n) Lee, D. Y. W.; He, M. S. *Curr. Top. Med. Chem.* **2005**, *5*, 1333. (o) Yuan, X.; Linhardt, R. J. *Curr. Top. Med. Chem.* **2005**, *5*, 1393. (p) Lin, C.-H.; Lin, H.-C.; Yang, W.-B. *Curr. Top. Med. Chem.* **2005**, *5*, 1431. (q) Adamo, M. F. A.; Pergoli, R. *Curr. Org. Chem.* **2008**, *12*, 1544. (r) Štambaský, J.; Hocek, M.; Kočovský, P. *Chem. Rev.* **2009**, *109*, 6729.

(2) (a) Findlay, J. A.; Lin, J.-S.; Radics, L.; Rachit, S. *Can. J. Chem.* **1981**, *59*, 3018. (b) Sehgel, S. N.; Czerkawski, H.; Kudelski, A.; Pander, K.; Saucier, R.; Vézina, C. *J. Antibiot.* **1983**, *36*, 355.

(3) Takahashi, K.; Yoshida, M.; Tomita, F.; Shirahata, K. *J. Antibiot.* **1981**, *34*, 271.

(4) (a) Daves, G. D. Jr. *Acc. Chem. Res.* **1990**, *23*, 201. (b) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545. (c) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700. (d) Isobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *Chem. Commun.* **1998**, 2665. (e) Smoliakova, I. P. *Curr. Org. Chem.* **2000**, *4*, 589. (f) Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263. (g) Zou, W. *Curr. Top. Med. Chem.* **2005**, *5*, 1363. (h) Saeeng, R.; Isobe, M. *Chem. Lett.* **2006**, *35*, 552. For recent reviews on C-glycoside biology and biosynthesis, see: (i) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077. (j) Hultin, P. G. *Curr. Top. Med. Chem.* **2005**, *5*, 1299. (k) Bililign, T.; Griffith, B. R.; Thorson, J. S. *Nat. Prod. Rep.* **2005**, *22*, 742. (l) Wellington, K. W.; Benner, S. A. *Nucleosides, Nucleotides Nucleic Acids* **2006**, *25*, 1309.

(5) For selected reviews and papers on coumarin derivatives and their biological applications, see: (a) Murray, R. D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins: Occurrence, Chemistry, and Biochemistry*; Wiley: Chichester, **1982**. (b) Murray, R. D. H. *Nat. Prod. Rep.* **1995**, *12*, 477. (c) O'Kennedy, R.; Thornes, R. D. *Coumarins: Biology, Applications and Mode of Action*; Wiley: Chichester, **1997**. (d) Sardari, S.; Nishibe, S.; Daneshtalab, M. *Stud. Nat. Prod. Chem.* **2000**, *23*, 335. (e) Murray, R. D. H. *Prog. Chem. Org. Nat. Prod.* **2002**, *83*, 1. (f) Garazd, M. M.; Garazd, Y. L.; Khilya, V. P. *Chem. Nat. Compd.* **2003**, *39*, 54. (g) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667. (h) Zhao, Y.; Zheng, Q.; Dakin, K.; Xu, K.; Martinez, M. L.; Li, W.-H. *J. Am. Chem. Soc.* **2004**, *126*, 4653. (i) Kuo, P.-Y.; Yang, D.-Y. *J. Org. Chem.* **2008**, *73*, 6455.

(6) Dubois, M.-A.; Wierer, M.; Wagner, H. *Phytochemistry* **1990**, *29*, 3369.
(7) Garazd, Y. L.; Kornienko, E. M.; Maloshtan, L. N.; Garazd, M. M.; Khilya, V. P. *Chem. Nat. Compd.* **2005**, *5*, 508.
(8) Burlison, J. A.; Avila, C.; Vielhauer, G.; Lubbers, D. J.; Holzbeierlein, J.; Blagg, B. S. J. *J. Org. Chem.* **2008**, *73*, 2130.
(9) (a) Musicki, B.; Periers, A.-M.; Piombo, L.; Laurin, P.; Klich, M.; Dupuis-Hamelin, C.; Lassaigne, P.; Bonnefoy, A. *Tetrahedron Lett.* **2003**, *44*, 9259. (b) Scatigno, A. C.; Garrido, S. S.; Marchetto, R. *J. Pept. Sci.* **2004**, *10*, 566.
(10) (a) Coleman, R. S.; Madaras, M. L. *J. Org. Chem.* **1998**, *63*, 5700. (b) Coleman, R. S.; Berg, M. A.; Murphy, C. J. *Tetrahedron* **2007**, *63*, 3450.
(11) For selected examples, see: (a) Sarker, S. D.; Waterman, P. G. *J. Nat. Prod.* **1995**, *58*, 1109. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (c) Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. *Curr. Med. Chem.* **2005**, *12*, 887. (d) Ngameni, B.; Touaibia, M.; Patnam, R.; Belkaid, A.; Sonna, P.; Ngadjui, B. T.; Anabi, B.; Roy, R. *Phytochemistry* **2006**, *67*, 2573. (e) Su, J.; Wu, Z.-J.; Zhang, W.-D.; Zhang, C.; Li, H.-L.; Liu, R.-H.; Shen, Y.-H. *Chem. Pharm. Bull.* **2008**, *56*, 589. (f) Akak, C. M.; Djama, C. M.; Nkengfack, A. E.; Tu, P.-F.; Lei, L.-D. *Fitoterapia* **2010**, *81*, 873.
(12) Batsurén, D.; Batirov, É. Kh.; Malikov, V. M.; Yagudaev, M. R. *Khim. Prir. Soedin.* **1983**, 142; *Chem. Nat. Compd.* **1983**, *19*, 134.
(13) (a) Batsurén, D.; Batirov, É. Kh.; Malikov, V. M. *Khim. Prir. Soedin.* **1982**, 650; *Chem. Nat. Compd.* **1983**, *18*, 616. (b) Vdovin, A. D.; Batsurén, D.; Batirov, É. Kh.; Yagudaev, M. R.; Malikov, V. M. *Khim. Prir. Soedin.* **1983**, 441; *Chem. Nat. Compd.* **1984**, *19*, 413. (c) Aminov, S. D.; Vakhabov, A. A. *Dokl. Akad. Nauk SSSR* **1985**, 44.
(14) Hirakura, K.; Saida, I.; Fukai, T.; Nomura, T. *Heterocycles* **1985**, *23*, 2239.
(15) (a) O'Callaghan, C. N.; Conalty, M. L. *Proc. R. Ir. Acad., Sect. B* **1979**, *6*, 87. (b) Burke, T. R. Jr.; Lim, B.; Marquez, V. E.; Li, Z.-H.; Bolen, J. B.; Stefanova, I.; Horak, I. D. *J. Med. Chem.* **1993**, *36*, 425.
(16) Mahling, J.-A.; Schmidt, R. R. *Liebigs Ann.* **1995**, 467.
(17) (a) Toshima, K.; Matsuo, G.; Ishizuka, T.; Ushiki, Y.; Nakata, M.; Matsumura, S. *J. Org. Chem.* **1998**, *63*, 2307. (b) Telbani, E. E.; Desoky, S. E.; Hammad, M. A.; Rahman, A. R. H. A.; Schmidt, R. R. *Eur. J. Org. Chem.* **1998**, 2317. (c) Oyama, K.; Kondo, T. *J. Org. Chem.* **2004**, *69*, 5240. (d) See also ref. 4k.
(18) Saha, N. N.; Desai, V. N.; Dhavale, D. D. *J. Org. Chem.* **1999**, *64*, 1715.
(19) (a) Giguère, D.; Patnam, R.; Juarez-Ruiz, J. M.; Neault, M.; Roy, R. *Tetrahedron Lett.* **2009**, *50*, 4254. (b) Giguère, D.; Cloutier, P.; Roy, R. *J. Org. Chem.* **2009**, *74*, 8480.
(20) For selected papers and reviews on multicomponent reactions, see: (a) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.–Eur. J.* **2000**, *6*, 3321. (b) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. (c) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133. (d) Marcaccini, S.; Miguel, D.; Torroba, T.; García-Valverde, M. *J. Org. Chem.* **2003**, *68*, 3315. (e) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899. (f) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223. (g) Byk, G.; Kabahn, E. *J. Comb. Chem.* **2004**, *6*, 596. (h) Liéby-Muller, F.; Constantieux, T.; Rodriguez, J. *J. Am. Chem. Soc.* **2005**, *127*, 17176. (i) Ramon, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602. (j) *Multicomponent Reactions*; Zhu, J.; Bienaymé, H., Eds.; Wiley-VCH: Weinheim, **2005**. (k) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
(21) (a) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038. (b) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046. (c) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347.
(22) For recent reviews, see: (a) Yoo, E. J.; Chang, S. *Curr. Org. Chem.* **2009**, *13*, 1766. (b) Lu, P.; Wang, Y.-G. *Synlett* **2010**, 165. (c) Kim, S. H.; Park, S. H.; Choi, J. H.; Chang, S. *Chem.–Asian J.* **2011**, *6*, 2618.
(23) (a) Chang, S.; Lee, M.; Jung, D. Y.; Yoo, E. J.; Cho, S. H.; Han, S. K. *J. Am. Chem. Soc.* **2006**, *128*, 12366. (b) Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 1730. (c) Cho, S. H.; Chang, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 1897. (d) Cho, S. H.; Chang, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 2836. (e) Yoo, E. J.; Ahlquist, M.; Bae, I.; Sharpless, K. B.; Fokin, V. V.; Chang, S. *J. Org. Chem.* **2008**, *73*, 5520. (f) Kim, J.; Lee, S. Y.; Lee, J.; Do, Y.; Chang, S. *J. Org. Chem.* **2008**, *73*, 9454. (g) Yoo, E. J.; Chang, S. *Org. Lett.* **2008**, *10*, 1163. (h) Hwang, S. J.; Cho, S. H.; Chang, S. *Pure Appl. Chem.* **2008**, *80*, 873. (i) Kim, J. Y.; Kim, S. H.; Chang, S. *Tetrahedron Lett.* **2008**, *49*, 1745. (j) Yoo, E. J.; Park, S. H.; Lee, S. H.; Chang, S. *Org. Lett.* **2009**, *11*, 1155. (k) Lee, M. Y.; Kim, M. H.; Kim, J.; Kim, S. H.; Kim, B. T.; Jeong, I. H.; Chang, S.; Kim, S. H.; Chang, S.-Y. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 541. (l) Husmann, R.; Na, Y. S.; Bolm, C.; Chang, S. *Chem. Commun.* **2010**, *46*, 5494.
(24) (a) Cui, S.-L.; Lin, X.-F.; Wang, Y.-G. *Org. Lett.* **2006**, *8*, 4517. (b) Cui, S.-L.; Wang, J.; Wang, Y.-G. *Org. Lett.* **2007**, *9*, 5023. (c) Cui, S.-L.; Wang, J.; Wang, Y.-G. *Org. Lett.* **2008**, *10*, 13. (d) Cui, S.-L.; Wang, J.; Wang, Y.-G. *Org. Lett.* **2008**, *10*, 1267. (e) Cui, S.-L.; Wang, J.; Wang, Y.-G. *Tetrahedron* **2008**, *64*, 487. (f) Lu, W.; Song, W.; Hong, D.; Lu, P.; Wang, Y.-G. *Adv. Synth. Catal.* **2009**, *351*, 1768. (g) She, J.; Jiang, Z.; Wang, Y.-G. *Synlett* **2009**, 2023. (h) Jin, H.; Xu, X.; Gao, J.; Zhong, J.; Wang, Y.-G. *Adv. Synth. Catal.* **2010**, *352*, 347. (i) Shen, Y.; Cui, S.; Wang, J.; Chen, X.; Lu, P.; Wang, Y.-G. *Adv. Synth. Catal.* **2010**, *352*, 1139. (j) Song, W.; Lei, M.; Shen, Y.; Cai, S.; Lu, W.; Lu, P.; Wang, Y.-G. *Adv. Synth. Catal.* **2010**, *352*, 2432. (k) Song, W.; Lu, W.; Wang, J.; Lu, P.; Wang, Y.-G. *J. Org. Chem.* **2010**, *75*, 3481. (l) Wang, J.; Wang, J.; Zhu, Y.; Lu, P.; Wang, Y.-G. *Chem Commun.* **2011**, *47*, 3275. (m) Li, Y.; Hong, D.; Zhu, Y.; Lu, P.; Wang, Y.-G. *Tetrahedron* **2011**, *67*, 8086.
(25) (a) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2006**, *45*, 3154. (b) Whiting, M.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2006**, *45*, 3157. (c) Mandal, S.; Gauniyal, H. M.; Pramanik, K.; Mukhopadhyay, B. *J. Org. Chem.* **2007**, *72*, 9753. (d) Xu, X.; Cheng, D.; Li, J.; Guo, H.; Yan, J. *Org. Lett.* **2007**, *9*, 1585. (e) Wang, F.; Fu, H.; Jiang, Y.; Zhao, Y. *Adv. Synth. Catal.* **2008**, *350*, 1830. (f) Shang, Y.; He, X.; Hu, J.; Wu, J.; Zhang, M.; Yu, S.; Zhang, Q. *Adv. Synth. Catal.* **2009**, *351*, 2709. (g) Yao, W.; Pan, L.; Zhang, Y.; Wang, G.; Wang, X.; Ma, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 9210. (h) Shang, Y.; Ju, K.; He, X.; Hu, J.; Yu, S.; Zhang, M.; Liao, K.; Wang, L.; Zhang, P. *J. Org. Chem.* **2010**, *75*, 5743. (i) Chen, Z.; Ye, C.; Gao, L.; Wu, J. *Chem. Commun.* **2011**, *47*, 5623. (j) Chen, Z.; Zheng, D.; Wu, J. *Org. Lett.* **2011**, *13*, 848. (k) Li, S.; Luo, Y.; Wu, J. *Org. Lett.* **2011**, *13*, 3190. (l) Li, S.; Luo, Y.; Wu, J. *Org. Lett.* **2011**, *13*, 4312. (m) Namitharan, K.; Pitchumani, K. *Org. Lett.* **2011**, *13*, 5728. (n) Liu, Y.; Wang, X.; Xu, J.; Zhang, Q.; Zhao, Y.; Hu, Y. *Tetrahedron* **2011**, *67*, 6294.

(26) (a) Kaliappan, K. P.; Subrahmanyam, A. V. *Org. Lett.* **2007**, *9*, 1121. (b) Kaliappan, K. P.; Kalanidhi, P.; Mahapatra, S. *Synlett* **2009**, 2162. (c) Subrahmanyam, A. V.; Palanichamy, K.; Kaliappan, K. P. *Chem.–Eur. J.* **2010**, *16*, 8545. (d) Khangarot, R. K.; Kaliappan, K. P. *Eur. J. Org. Chem.* **2011**, 6117.

(27) (a) Betkekar, V. V.; Panda, S.; Kaliappan, K. P. *Org. Lett.* **2012**, *14*, 198. (b) Alkyne **10** was synthesized by methylation of the corresponding propargylic tertiary alcohol, see: Ramana, C. V.; Mallik, R.; Gonnade, R. G. *Tetrahedron* **2008**, *64*, 219.

