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Theoretical Study of 1,3-Dipolar Cycloaddition of Hydrazoic Acid to Substituted Ynamines†

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The 1,3-dipolar cycloaddition reactions of various substituted ynamines with hydrazoic acid were theoretically investigated with the high-accuracy CBS-QB3 method. Two regioisomers, 4-amine, and 5-amine substituted adducts, were obtained, with the former as the preferred yield. This regioselectivity is rationalized by the frontier molecular orbital theory. The reactivity and synchronicity are enhanced with the increase of the electron-withdrawing character of the substitute on ynamine fragment. The calculations also show that the effect of solvent increases the activation energy, and the reaction becomes even harder in polar solvent.

Key words: 1,3-dipolar cycloaddition, Hydrazoic acid, Internal alkyne, CBS-QB3, Solvent effect, Substituent effect, Frontier molecular orbital theory

I. INTRODUCTION

1,2,3-triazole series have received considerable attention in chemistry, biology, medicinal chemistry, and material science [1-8]. Huisgen's 1,3-dipolar cycloaddition of azides with alkynes is the most common strategy of synthesizing 1,2,3-triazole series [6,8-10]. The copper-catalyzed azides with terminal acetylenes provides accesses to 1,4-disubstituted-1,2,3-triazole. But ruthenium promoted unions of the terminal alkynes and azide yield exclusively 1,5-disubstituted-1,2,3-triazole regioisomers [11-14]. The internal alkynes are also the building blocks in synthesizing 1,2,3-triazoles, as promoted by ruthenium catalysts [11]. Copper catalysts, based on N-heterocyclic carbine (NHC) templates, are capable of catalyzing azide cycloadditions involving both terminal and internal alkynes [15]. Recently, ruthenium-catalyzed Huisgen cycloaddition of ynamides has been conducted, which yields only 1,5-disubstituted triazole isomer, showing a complete regioselectivity [16]. Metal-free triazole formation as a tool for bioconjugation has been applied to ligate several bio(macro)molecules under physiological conditions [7,17-21].

A stepwise mechanism involving unprecedented metallacycle intermediates is proposed to interpret the exquisite selectivity in the copper-catalyzed synthesis of azoles [9]. An irreversible oxidative coupling process accounts for the regioselectivity in the ruthenium-catalyzed azide-alkyne cycloaddition [11]. The electron-rich alkynes are more easily reacted with azides than the electron-deficient alkynes [22], and the predicted narrow range of activation enthalpies (71.1-87.8 kJ/mol) is associated with formylazide cycloadditions with various terminal alkenes and alkynes. The azide-alkyne cycloadditions are under a large thermodynamic driving force.

This study will focus on the 1,3-dipolar cycloaddition of a series of internal alkynes with hydrazoic acid (HN_3). Herein, internal alkynes are selected as various substituted ynamines (SY-R). The aim is to use the high-accuracy complete basis set(CBS)-QB3 method to predict the substituent effects on the reactivity and regioselectivity in the title reactions. The goal is to provide the computational preliminary work for metal-free synthesis of triazole in the future.

II. COMPUTATIONAL DETAILS

All geometry and energy were performed by using the CBS-QB3 method as implemented in the Gaussion03 suite of programs [23]. CBS-QB3 involves optimizations with the B3LYP method and the 6-311G(2d,d,p) basis set. A series of higher level calculations are performed with this geometry, such as CCSD(T), MP4, and MP2. The conductor-like polarized continuum model with the self-consistent reaction field (CPCM-SCRF) is utilized to predict the solvent effects of all stationary points found with CBS-QB3. All the stationary points are optimized without imposing any symmetrical restriction in the gas phase and solutions at standard temperature and pressure. The transition states (TSs) are verified by

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TABLE I Net natural bond orbital charge (in e) of the transition states of some atoms (The atomic numbering is shown in Fig.1).

−R	4-amine substituted process TS					5-amine substituted process TS				
	Δd[a]	N1	N3	C4	C5	Δd[a]	N1	N3	C4	C5
−OH	0.838	−0.101	−0.672	0.252	0.247	0.371	−0.065	−0.631	0.410	0.016
$-CH_3$	0.598	−0.101	−0.666	0.355	−0.127	0.191	−0.060	−0.582	0.015	0.100
−H	0.581	−0.092	−0.662	0.363	−0.332	−0.218	−0.051	−0.552	−0.251	0.129
$-CONH_2$	0.463	−0.082	−0.621	0.436	−0.309	−0.216	−0.050	−0.500	−0.237	0.213
$-NO_2$	0.438	0.000	−0.611	0.393	−0.073	−0.350	−0.003	−0.516	−0.009	0.217

[a] The bond length difference (in Å), i.e., Δd=R(N3−C4)−R(N1−C5).

TABLE II Activation enthalpies ($\Delta H^{\neq}$), reaction enthalpies (ΔH_r), activation free energies ($\Delta G^{\neq}$), and reaction free energies (ΔG_r) for the 1,3-dipolar cycloaddition of hydrazoic acid to substituted ynamine calculated by CBS-QB3 (energies are in kJ/mol.).

−R	4-amine substituted process					5-amine substituted process				
	Q_{NPA}[a]	$\Delta H^{\neq}$	$\Delta G^{\neq}$	ΔH_r	ΔG_r	Q_{NPA}[a]	$\Delta H^{\neq}$	$\Delta G^{\neq}$	ΔH_r	ΔG_r
−OH	0.282	86.5	135.0	−302.2	−245.4	0.159	96.6	143.8	−322.3	−265.4
$-CH_3$	0.275	85.3	131.7	−278.4	−223.6	0.081	93.6	138.4	−270.4	−217.4
−H	0.260	78.6	127.9	−277.1	−220.3	0.031	93.6	139.6	−267.9	−211.1
$-CONH_2$	0.159	62.7	116.2	−302.2	−239.1	−0.087	78.6	129.2	−314.8	−251.6
$-NO_2$	0.051	53.5	106.2	−329.0	−265.8	−0.140	76.5	128.3	−325.2	−260.0

[a] The sum of bond orbital charge (in e) on the atoms of dipolarophiles at the transition structures for the 1,3-dipolar cycloaddition of hydrazoic acid to substituted ynamine, based on natural population analysis (NPA).

vibrational analysis with only one imaginary frequency mode. The imaginary frequency mode in TSs has been checked to correspond with a movement in the direction of the reaction coordinate [24].

III. RESULTS AND DISCUSSION

A. Geometries of the transition structures

Figure 1 illustrates the 1,3-dipolar cycloaddition of hydrazoic acid to substituted ynamines. This process can give rise to two regioisomers, which are 4-amine and 5-amine substituted adducts. The optimized transition structures are shown in Fig.2, as calculated by the CBS-QB3 method. The analysis of the vibration of the imaginary frequency in TSs indicates that the formation of the N3−C4 and N1−C5 bonds is concerted. However, the lengths of the N1−C5 bond in transition structures are remarkably different from those of the N3−C4 bond. Obviously, the 1,3-dipolar cycloaddition of hydrazoic acid with substituted ynamines is based on a highly asynchronous concerted mechanism. This asynchronicity can be measured by the bond length difference between the two forming bonds in transition structures, i.e. Δd=R(N3−C4)−R(N1−C5). As shown in Table I, (i) the length of N3−C4 bond is always longer than that of the N1−C5 bond for 4-aimine substituted transition states, whereas for 5-aimine substituted transition states, N3−C4 bond is shorter than N1−C5 bond for −H, $-CONH_2$, and $-NO_2$ substituted ynamines; (ii) the greater the electron-withdrawing character of the substituted group is, the less the value of Δd is; (iii) the absolute value of Δd for 4-amine substituted transition structure always exceeds that for the corresponding 5-amine substituted transition structure.

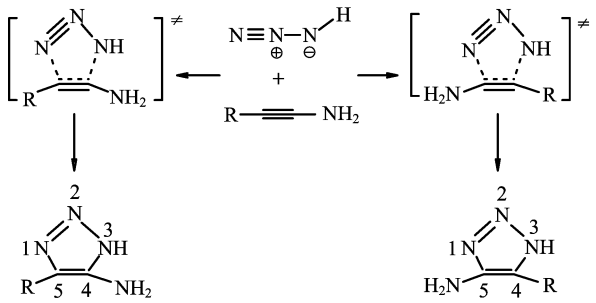

FIG. 1 The 1,3-dipolar cycloaddition of the hydrazoic acid (HN_3) to the substituted ynamine (SY) to yield two regioisomeric adducts.

B. Activation energy and regioselectivity

Table II shows that the activation enthalpies in the gas phase are 53.5-96.6 kJ/mol for the title reactions.

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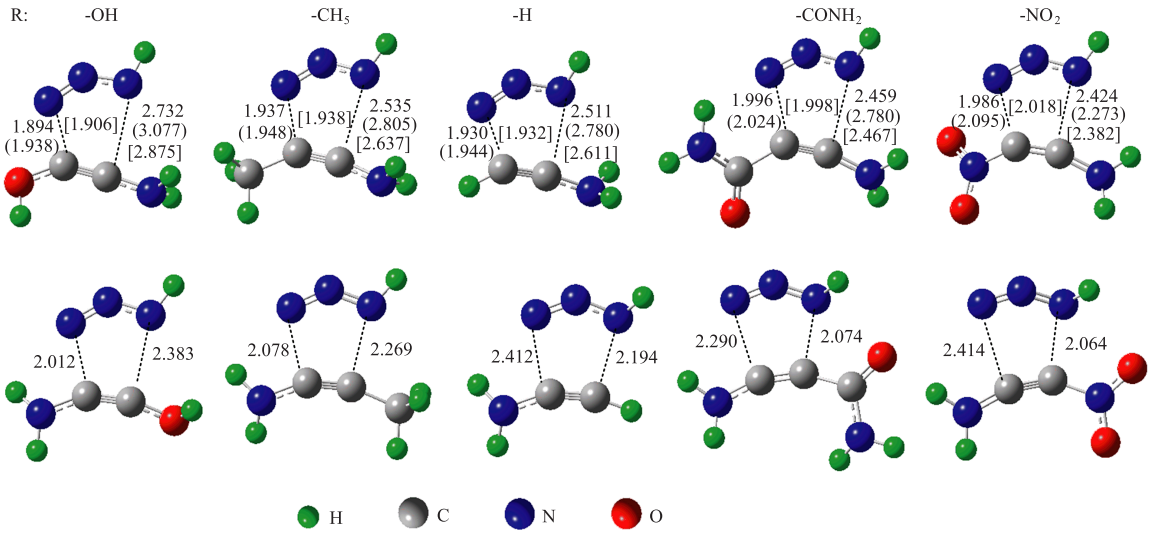

FIG. 2 The optimized transition structures in the gas phase and solutions based on CBS-QB3 method. Bond lengths (in Å) shown in parentheses and square brackets are in aqueous solvent and benzene, respectively. The blue, red, green, and gray balls are N, O, H, and C atoms. For interpretation of the color in this figure legend, the reader can refer to the web version of this article.

The similar cycloaddition of hydrazoic acid to ethane, acetylene, formaldimine, and HCN was reported to have the activation enthalpies of 79.8, 79.8, 90.7, and 105.8 kJ/mol respectively.[25] The activation/reaction enthalpies are 78.6/-277.1 and 93.6/-267.9 kJ/mol for the formation of 4-amine and 5-amine adducts in the 1,3-dipolar cycloaddition of hydrazoic acid to ynamine (i.e. R=−H), respectively. They are close to the values (79.4/-266.3 kJ/mol) for the cycloaddition of hydrazoic acid to acetylene in previous theoretical studies [22]. But triazoles from the reactions of various substituted ynamine and hydrazoic acid are ∼167.0 kJ/mol more stable than triazoline from the cycloaddition of azide to terminal alkene. In the cycloaddition of methyl azide to propyne, the activation barrier was found to be ∼107.4 and 108.7 kJ/mol for affording both 1,4- and 1-5 regioisomers of the 1,2,3-triazole without the catalyst, while it was 62.6 kJ/mol for the copper(I)-catalyzed synthesis of 1,4-regioisomers [9]. By comparison, the calculated activation enthalpy is 62.7/53.5 kJ/mol for the cycloadditions of hydrazoic acid to amide/nitro substituted ynamine, as shown in Table II. We can predict that the reactivity of hydrazoic acid with amide/nitro substituted ynamine is almost equivalent to/greater than that of the copper(I)-catalyzed methyl azide and propyne.

The activation enthalpy differences between 4-amine and 5-amine substituted reactions are 8.4-12.5 and 23.0 kJ/mol for reactions involving electron-donating (R=−OH, $-CH_3$) and electron-withdrawing (R=$-NO_2$) substituted ynamines, respectively. Also, they are ∼16.7 kJ/mol for reactions involving conjugated ynamines (R=−H and $-CONH_2$). Apparently, the 1,3-dipolar cycloaddition of hydrazoic acid to various substituted ynamines has a preference for yielding 4-amine substituted adducts, and also this regioselectivity is enhanced with the increase of electron-deficient substituted ynamines. The previous experiments indicated that azide reacted with highly electron-deficient terminal alkynes exhibit good regioselectivity in the uncatalyzed Huisgen type cycloaddtion, while reactions with other alkynes usually afford mixtures of the 1,4- and 1,5-regioisomers [26,27]. Our calculated results on regioselectivity are compared with those experimental results.

C. Substituent effects

Substitution of ynamines with electron-withdrawing, electron-donating, and conjugating substituents exerts a powerful influence on activation barriers and reaction heats in the 1,3-dipolar cycloaddition of hydrazoic acid and various substituted ynamines. The reactions that involve electron-deficient (e.g. R=$-NO_2$) substituted ynamines have lower activation barriers than those involving electron-donating (e.g. R=−OH and $-CH_3$) substituted ynamines. For the reactions of ynamines with conjugating (e.g. R=−H and $-CONH_2$) groups, the reactivity is between those of ynamines with electron-donating and electron-withdrawing groups.

D. Natural population analysis

The charge distributions on atoms associated with two forming bonds allow us to clearly understand the chemical process. Natural population analysis (NPA) was carried out in terms of localized electron-pair "bonding" units. Table I lists the net natural bond

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orbital charge of the transition structure of some atoms (for the atomic numbering, refers to Fig.1). For example, if R=$-CH_3$, the net charges are -0.666e, 0.355e, -0.101e, and -0.127e on the N3, C4, N1, and C5 atoms in 4-amine substituted transitions state, while they are -0.582e, 0.015e, -0.060e, and 0.100e in the corresponding 5-amine substituted regioisomer, respectively. In two regioisomeric transition states, the N3 atom holds more net negative charges, while the N1 atom possesses less net negative charges. The net positive charges are partially on the C4 atom in 4-amine TSs, while they are on the C5 atom in the 5-amine substituted TSs. The charge distribution on the N3 and N1 atoms in 4-amine substituted TSs is larger than that in the corresponding 5-amine substituted regioisomers. The same case occurs for the positive charge sites. It is more likely that the 4-amine substituted transition states can be regarded as zwitterionic transition states, which are formed by the interaction between the positive ion of the C4 atom and the negative ion of the N3 atom, as shown in Fig.3.

The charge separations are also provided, which are listed in Table II. $Q_{\rm NPA}$ refers to the sum of bond orbital charge on the atoms of dipolarophiles (i.e. substituted ynamines) at the transition structures for the 1,3-dipolar cycloadditions of hydrazoic acid to substituted ynamines, based on the NPA. The values of $Q_{\rm NPA}$ are 0.282e (0.159e), 0.275e (0.081e), 0.260e (0.031e), 0.159e (-0.087e), and 0.051e (-0.140e) when the substituent groups are $-OH$, $-CH_3$, $-H$, $-CONH_2$, and $-NO_2$ in 4(5)-amine substituted TSs, respectively. Obviously, the electron-withdrawing ability of substituent groups in ynamines can accelerate the decrease of the charge transfer from substituted ynamine moiety to hydrazoic acid moiety at the transition states. Notably, the direction of the charge transfer is reversed by the stronger electron-deficient groups ($-CONH_2$, and $-NO_2$) in 5-amine substituted TSs. The trend in the charge transfer parallels the activation enthalpy variation for these reactions involving substituted ynamines. Thus, we can conclude that the smaller the $Q_{\rm NPA}$ is, the more active the substituted ynamines in the 1,3-dipolar cycloaddition to hydrazoic acid.

E. Frontier molecular orbital analysis

The frontier molecular orbital (FMO) mode is universally applied to explain the substituted effect for these inverse-electron-demand cycloaddition. Figure 4 presents the FMOs on the cycloaddition of the hydrazoic acid to various substituted ynamines. Here, we use denotations such as SY-OH, which refers to hydroxyl substituted ynamine. As shown in Fig.4, the $HOMO_{HN_3}$ of the hydrazoic acid is rather lower with an orbital energy of -7.60 eV, less than that of the SY-OH (-5.78 eV), SY-CH_3 (-5.72 eV), SY-H (-6.16 eV), SY-$CONH_2$ (-6.52 eV), and SY-NO_2 (-7.42 eV). The $LUMO_{HN_3}$ of the hydrazoic acid (-0.98 eV) is slightly below that of the SY-OH (0.61 eV), SY-CH_3 (0.86 eV), SY-H (0.70 eV), and SY-$CONH_2$ (-0.07 eV) in energy, while it is above that of SY-NO_2 (-2.20 eV). When the substituent group R is $-OH$, $-CH_3$, $-H$, or $-CONH_2$, the energy difference between $HOMO_{HN_3}$ of hydrazoic acid and $LUMO_{SY-R}$ of the substituted ynamines is greater than that between $HOMO_{SY-R}$ and $LUMO_{HN_3}$. Thus, the dominant interaction is between $HOMO_{SY-R}$ of these substituted ynamines and $LUMO_{HN_3}$ of hydrazoic acid. Otherwise, the main HOMO-LUMO interaction occurs between $LUMO_{SY-NO_2}$ of nitro substituted ynamine and $HOMO_{HN_3}$ in 1,3-dipolar cycloaddition of the nitro substituted ynamines to hydrazoic acid. Judging from Fig.4, the cycloaddition of SY-NO_2 and HN_3 has the best reactivity and the lowest activation energy. The presence of electron-withdrawing group decreases the electron distribution of substituted ynamine and makes $LUMO_{SY-R}$-$HOMO_{HN_3}$ the main interaction, leading to an improvement of the reactivity. According to the FMO theory on the reverse-electron-demand cycloaddition, it is easily predicted that electron-denoting groups on the hydrazoic acid will make a contribution to the shrinkage of HOMO-LUMO separation.

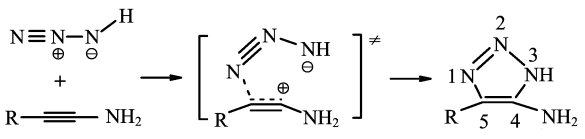

FIG. 3 Mechanism of the 4-amine substituted transition states.

F. Solvent effects

To understand the role of the solvent on the title cycloaddition, the CPCM mode was carried out in aque-

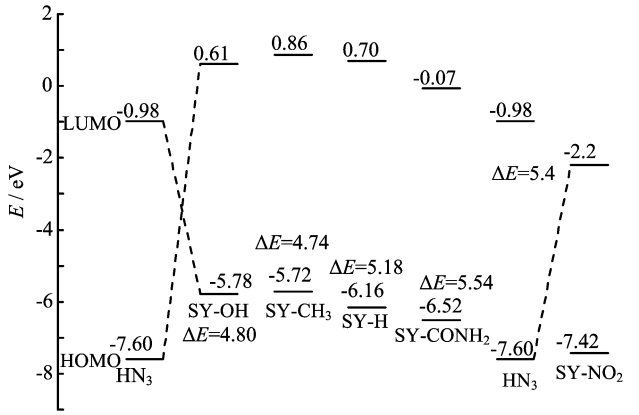

FIG. 4 Frontier molecular orbitals on the cycloaddition reaction between the hydrazoic acid and various substituted ynamines (Noting denotations such as SY-OH referring to the hydroxyl substituted ynamine).

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ous solvent (ε=78.39) and benzene (ε=2.247). As 4-amine substituted process is the preferred reaction of the 1,3-dipolar cycloaddition of hydrazoic acid to substituted ynamines, we focus on this channel in this subsection. The optimized structures of transition states are shown in Fig.2. For example, in 4-amine substituted transition state, if R=$-CH_3$, the distance of the N3−C4/N1−C5 bond is 2.805/1.948 and 2.637/1.938 Å in aqueous solvent and benzene, respectively, which is stretched in the comparison with that in the gas phase (2.535/1.937 Å). A similar trend also appears in the cycloaddition involving the non-substituted and hydroxyl substituted ynamines. The exception is the N3−C4 bond of amide substituted ynamine in aqueous solvent and N3−C4 bond of nitro substituted ynamine in aqueous solvent and benzene, which are shortened with respect to the corresponding values in the gas phase.

Table III lists the calculated energies and Δd in solvents. For the reactions involving electron-donating (e.g. R=$-$OH and $-CH_3$) substituted ynamines, the bond length difference, Δd, increases compared with that in the gas phase, indicating an enhancement of the asynchronicity of these reactions. In contrast, for the reaction involving electron-deficient (e.g. R=$-NO_2$) substituted ynamines, Δd decreases relative to that in the gas phase, which weakens the asynchronicity.

A comparison of the energy differences ($\Delta\Delta H^{\neq}$ and $\Delta\Delta G^{\neq}$) of the TSs in the gas phase and in solvents shows that with the inclusion of the solvent effect, there is an increase of the activation enthalpies and activation free energies. Moreover, for all substituted ynamines, except for the nitro substituted one, the cycloaddition in polar solvent (aqueous solvent) has an even higher activation barrier than that in very nonpolar solvent (benzene). These findings indicate that nonpolar solvents may be appropriate for this kind of reaction.

TABLE III Solvent effect of the aqueous solvent and benzene (in parentheses) for the 1,3-dipolar cycloadditions of hydrazoic acid to substituted ynamines.

−R	4-amine substituted process				
	Δd[a]	$\Delta\Delta H^{\neq}$[b]	$\Delta\Delta G^{\neq}$[c]	$\Delta\Delta H_r$[d]	$\Delta\Delta G_r$[e]
−OH	1.139	15.5	12.5	−24.7	−19.6
	(0.969)	(15.0)	(12.5)	(−23.0)	(−18.0)
$-CH_3$	0.857	22.6	18.8	−9.2	−9.2
	(0.699)	(16.3)	(13.8)	(2.1)	(1.3)
−H	0.836	28.0	23.8	−8.8	−8.4
	(0.679)	(22.2)	(18.8)	(2.1)	(2.5)
$-CONH_2$	0.376	31.4	26.3	−1.3	−1.3
	(0.469)	(26.3)	(24.7)	(−6.3)	(−4.6)
$-NO_2$	0.178	21.3	21.3	−5.0	−6.7
	(0.364)	(25.5)	(25.5)	(−13)	(3.3)

[a] The bond length difference is in Å, i.e. Δd=R(N3−C4)−R(N1−C5).
[b] $\Delta\Delta H^{\neq}$=$\Delta H^{\neq}$(solution)−$\Delta H^{\neq}$(gas) (in kJ/mol).
[c] $\Delta\Delta G^{\neq}$=$\Delta G^{\neq}$(solution)−$\Delta G^{\neq}$(gas) (in kJ/mol).
[d] $\Delta\Delta H_r$ =ΔH_r(solution)−ΔH_r(gas) (in kJ/mol).
[e] $\Delta\Delta G_r$=ΔG_r(solution)−ΔG_r(gas) (in kJ/mol).

IV. CONCLUSION

The high-accuracy CBS-QB3 method was used to study the 1,3-dipolar cycloaddition of hydrazoic acid to substituted ynamines. Hydrazoic acid cycloaddition with electron-deficient substituted ynamines has lower barriers than those with electron-donating and conjugated substituted ynamines. Energy calculations reveal that the 4-amine substituted channel is more favorable than the 5-amine substituted one. This regioselectivity is in accordance with the FMO analysis.

The calculations also indicate that, despite of the dielectric constants of the solvents, solvent effects increase the activation energy of the cycloaddition. In addition, the activation energy increases with the enhancement of the dielectric constant of the solvent, implying that this 1,3-dipolar cycloaddition is best conducted in nonpolar solvents.

V. ACKNOWLEDGMENT

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[1] G. C. Tron, T. Pirali, R. A. Billington, P. L. Canonico, G. Sorba, and A. A. Genazzani, Med. Res. Rev. **28**, 278 (2008).
[2] W. H. Binder, and R. Sachsenhofer, Macromol. Rapid Comm. **28**, 15 (2007).
[3] W. H. Binder, and R. Sachsenhofer, Macromol. Rapid Comm. **29**, 952 (2008).
[4] C. D. Hein, X. M. Liu, and D. Wang, Pharm. Res. **25**, 2216 (2008).
[5] M. Whiting, J. C. Tripp, Y. C. Lin, W. Lindstrom, A. J. Olson, J. H. Elder, K. B. Sharpless, and V. V. Fokin, J. Med. Chem. **49**, 7697 (2006).
[6] H. C. Kolb, M. G. Finn, and K. B. Sharpless, Angew. Chem. Int. Ed. **40**, 2004 (2001).
[7] A. Tam, U. Arnold, M. B. Soellner, and R. T. Raines, J. Am. Chem. Soc. **129**, 12670 (2007).
[8] M. Meldal and C. W. Tornoe, Chem. Rev. **108**, 2952 (2008).
[9] F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, and V. V. Fokin, J. Am. Chem. Soc. **127**, 210 (2005).
[10] R. Pereira de Freitas, J. Iehl, B. Delavaux-Nicot, and J. F. Nierengarten, Tetrahedron **64**, 11409 (2008).
[11] B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. T. Zhao, Z. Y. Lin, G. C. Jia, and V. V. Fokin, J. Am. Chem. Soc. **130**, 8923 (2008).

DOI:10.1088/1674-0068/22/02/143-148

[12] Y. B. Zhou, Z. F. Ke, and C. Y. Zhao, Acta Chim. Sin. **64**, 2071 (2006).
[13] K. Villeneuve and W. Tam, Eur. J. Org. Chem. 5449 (2006).
[14] L. K. Rasmussen, B. C. Boren, and V. V. Fokin, Org. Lett. **9**, 5337 (2007).
[15] S. Dez-Gonzlez, A. Correa, L. Cavallo, and S. P. Nolan, Chem. Eur. J. **12**, 7558 (2006).
[16] S. Oppilliart, G. Mousseau, L. Zhang, G. C. Jia, P. Thuery, B. Rousseau, and J. C. Cintrat, Tetrahedron **63**, 8094 (2007).
[17] W. G. Lewis, L. G. Green, F. Grynszpan, Z. Radic, P. R. Carlier, P. Taylor, M. G. Finn, and K. B. Sharpless, Angew. Chem. Int. Ed. **41**, 1053 (2002).
[18] A. Krasinski, Z. Radic, R. Manetsch, J. Raushel, P. Taylor, K. B. Sharpless, and H. C. Kolb, J. Am. Chem. Soc. **127**, 6686 (2005).
[19] S. S. van Berkel, A. T. J. Dirks, M. F. Debets, F. L. van Delft, J. Cornelissen, R. J. M. Nolte, and F. Rutjes, Chembiochem **8**, 1504 (2007).
[20] S. S. van Berkel, A. T. J. Dirks, S. A. Meeuwissen, D. L. L. Pingen, O. C. Boerman, P. Laverman, F. L. van Delft, J. Cornelissen, and F. Rutjes, Chembiochem **9**, 1805 (2008).
[21] R. Manetsch, A. Krasinski, Z. Radic, J. Raushel, P. Taylor, K. B. Sharpless, and H. C. Kolb, J. Am. Chem. Soc. **126**, 12809 (2004).
[22] G. O. Jones and K. N. Houk, J. Org. Chem. **73**, 1333 (2008).
[23] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, P. Salvador, J. J. Dannenberg, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, *Gaussian 03, Revision D.01*, Wallingford, CT: Gaussian, Inc., (2004).
[24] C. Gonzalez and H. B. Schlegel, J. Chem. Phys. **90**, 2154 (1989).
[25] G. O. Jones, D. H. Ess, and K. N. Houk, Helv. Chim. Acta **88**, 1702 (2005).
[26] K. V. Gothelf and K. A. Jorgensen, Chem. Rev. **98**, 863 (1998).
[27] D. Clarke, R. W. Mares, and H. McNab, J. Chem. Soc. Perkin Trans. **1**, 1799 (1997).

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