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Direct, Catalytic Synthesis of Carbapenams via Cycloaddition/Rearrangement Cascade Reaction: Unexpected Acetylenes' Structure Effect

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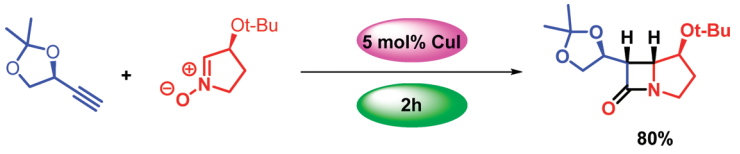


Reactions of acetylenes derived from glyceraldehyde and propargyl aldehyde show remarkable reactivity in Kinugasa cycloaddition/rearrangement cascade process catalyzed by Cu(I) ion. Reactions proceed by formation of a rigid dinuclear copper(I) complex in which each copper ion is coordinated to one or both oxygen atoms in the acetylene molecule and to both triple bonds. It has been demonstrated that one oxygen atom can be replaced by the phenyl ring, which is able to coordinate the copper ion by the aromatic sextet. Kinugasa reactions that proceed in a high yield can also be performed in the presence of a catalytic amount of the copper salt to provide products in an acceptable yield without a decrease of diastereoselectivity.

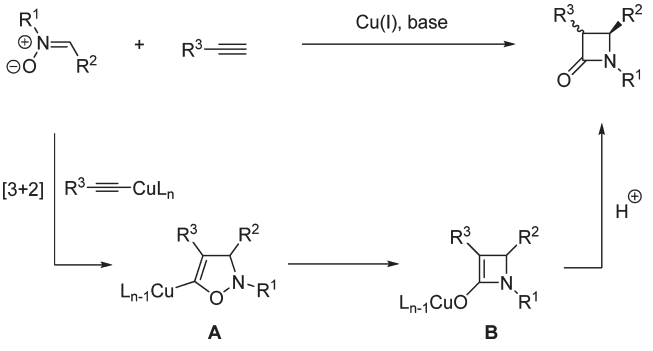
Introduction

2-Azetidinones are synthetic targets of a great biological importance because of their presence in antibiotics, such as penicillins and cephalosporins,[1] anticancer agents,[2] and cholesterol absorbance inhibitors.[3] β-Lactams have also been used as attractive building blocks in the stereocontrolled synthesis of complex organic compounds.[4] Preparation of the paclitaxel β-amino acid side chain has been an excellent example of the application of a β-lactam synthon as an intermediate in target-oriented synthesis.[5] The importance of β-lactam compounds maintains a high level of interest in methods of their synthesis at academic and industrial laboratories.

Among numerous direct methodologies leading to chiral β-lactams,[1,4,6] the copper-mediated reaction of nitrones with terminal alkynes (known as the Kinugasa reaction[7]) has received increased attention during the past decade.[8−12]

As shown in Scheme 1, Kinugasa reaction is a cycloaddition/rearrangement cascade process catalyzed by Cu(I) ion, which proceeds in the presence of organic base. The initially formed copper-alkyne π-complex undergoes deprotonation. Such activated triple bond is subjected to the 1,3-dipolar

SCHEME 1. Proposed Mechanism of the Kinugasa Reaction



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(1) (a) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 1−3. (b) *Synthesis of β-Lactam Antibiotics*; Bruggink, A., Ed.; Kluwer: Dordrecht, Netherlands, 2001.

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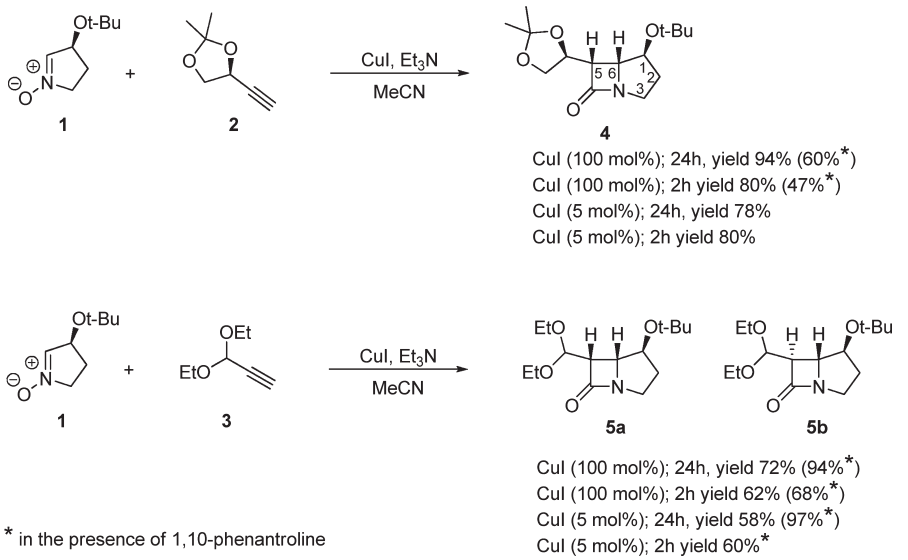
SCHEME 2. Reaction of Nitrone 1 with Acetylenes 2 and 3



cycloaddition with a nitrone to provide a five-membered isoxazoline **A**. Rearrangement of the isoxazoline copper complex **A** to the copper enolate **B** and its subsequent protonation leads to the formation of the β-lactam ring.

Although the first examples of the Kinugasa reaction were described in the 1970s,[7,9a] almost three decades passed before the reaction received more attention and has been explored in detail. Nevertheless, the number of reports related to this area of direct formation of 2-azetidinones, both in diastereo-[8,11] and enantioselective[8,12] variants, is still limited. Moreover, in most known cases, the *C*,*N*-diarylnitrones have been applied almost exclusively.[8−10,12] The examples of reactions involving aliphatic nitrones are rare.[9a,11]

As we demonstrated recently,[11] the reaction of cyclic aliphatic nitrones (e.g., **1** readily available from malic acid[13]) with terminal acetylenes, both achiral[11a] or enantiomerically defined,[11b] leads to carbapenams with a high stereoselectivity. The yields of desired products varies from poor, for aliphatic acetylenes, to moderate and good for aryl acetylenes. Interestingly, somewhat better results have been observed for certain aliphatic acetylenes bearing oxygen atoms.[11] The effectiveness of these reactions in several cases can be further slightly enhanced by addition of hydrazine,[11a] or *N*,*N*-ligands, such as 2,2′-bipyridine or 1,10-phenantroline.[9c,14] The latter has also been used as an activator in cycloaddition of azides to terminal acetylenes, known as click-reaction (Scheme 2).[15]

On the basis of our experience with cycloadditions involving nitrones, we assumed that the main reason for the less than satisfactory yield of Kinugasa reaction is its low rate. It has been proposed that the first step of the cascade, the 1,3-dipolar cycloaddition, is slow and reversible.[8,16] The second step—the rearrangement of copper−isoxazoline into enolate—is also slow due to the high energy barrier of contraction of the five-membered isoxazoline ring into the smaller, four-membered 2-azetidine enolate ring. Due to the low rate of these processes, the side-reactions involving multiple pathways of reactivity of nitrone, for example their deoxygenation by copper ion,[16,17] as well as copper-mediated acetylene coupling,[18] may occur. It should be pointed out that our attempts to exchange copper by silver or gold ion were unsuccessful; we did not observe any reaction.

Results and Discussion

During our ongoing research on the synthesis of β-lactams *via* Kinugasa cycloaddition/rearrangement cascade, we found that acetylene **2**, derived from D-glyceraldehyde acetonide, displayed a remarkable reactivity in comparison to other acetylenes (Scheme 2). Enhanced reactivity has also been observed for the propargyl-diethoxy acetal **3** (Scheme 2). The unexpected positive

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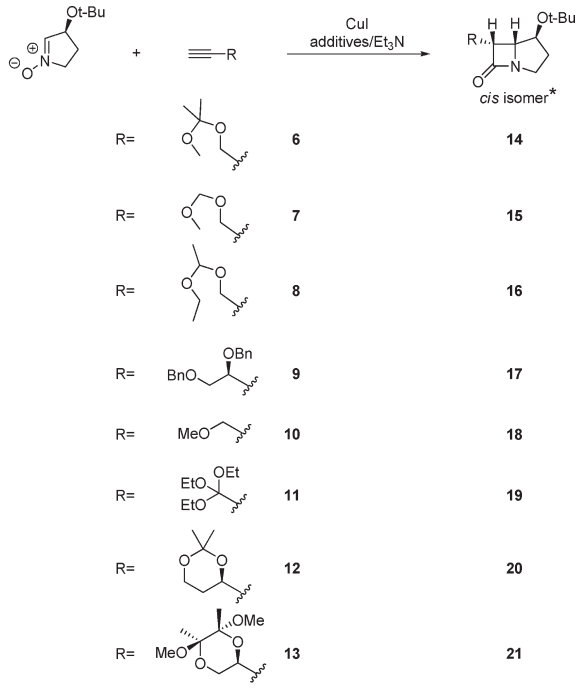
SCHEME 3. Reactions of Nitrone 1 with Acetylenes 6−13



* in all cases more than 95% of *cis* isomer was obtained

result of the Kinugasa reaction found for these acetylenes encouraged us to investigate the structure−reactivity relationship of acetylenes.

We were able to confirm that the effectiveness of acetylene components in the Kinugasa reaction can be improved by addition of 1,10-phenatroline.[14] In the case of acetylenes investigated by us earlier,[11] an addition of 1,10-phenatroline or 2,2′-bipyridine resulted in only a small improvement of reaction yield (about 5−10%), however. The largest increase of the reaction yield was noticed for the acetal **3**, (an increase from 72 to 94%). The same change applied to the reaction of **1** with **2** unexpectedly decreased the yield.

Further studies showed that reactions involving acetylenes **2** and **3** were more effective than we expected. We found that after just 2 h both processes afforded desired products in good yields, 80% in the case of **2** and 68% in the case of **3**, with stochiometric amounts of CuI. The remarkable reactivity of **2** was further demonstrated by catalytic experiments; in the presence of 5 mol % of CuI, reaction with **1** proceeded in 80% after 2 h and in 78% yield after 24 h. It indicates that the substrates were likely consumed in 2 h or less. Reaction of **3** under analogous conditions appeared to be slightly less effective and the mixture of diastereoisomeric products **5** were obtained in 60−70% yield (Scheme 2). Once again, the addition of 1,10-phenantroline (5 mol %) enhanced catalytic process significantly to afford **5** in 60% (after 2 h) and 97% (after 24 h) yield, respectively.

For extended studies on the acetylenes' structure−reactivity relationship, several acetylenes (**6**−**13**) structurally related to **2** and **3** have been chosen (Scheme 3). Compounds **6**−**13** were obtained according to known procedures, from propargyl alcohol: *via* an acid catalyzed acetal exchange (**6** and **8**),[19]

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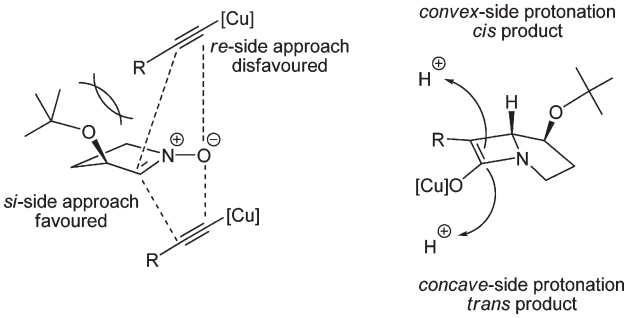

FIGURE 1. Stereochemical outcome of the Kinugasa reaction.

by treatment with methoxymethyl chloride in presence of a base (**7**),[19] or by methylation (**10**); from D-glyceraldehyde to **9**;[20] from trimethylsilyl-acetylene to **11**;[21] from D-malic acid to **12**;[22,23] and from D-mannitol to **13**.[24] Reactions between nitrone **1** and acetylenes **6**−**13** were performed under our standard conditions to afford the corresponding carbapenams **14**−**21**. Bearing in mind that Kinugasa reactions are sometimes capricious or sensitive to small changes of reaction conditions, every experiment was repeated.

The observed stereochemical outcome of all new investigated reactions was the same as for previous cases investigated by us.[11] The acetylene copper complex approaches the nitrone **1** molecule exclusively *anti* to *tert*-butoxy substituent present in the 1,3-dipole to provide the corresponding carbapenams **14**−**21** (Figure 1). The *cis* substitution of β-lactam ring is observed either exclusively, or it significantly dominates since the protonation of the copper enolate proceeds from less shielded convex-side of the carbapenam skeleton (Figure 1).[11a] The typical amount of *trans* diastereoisomers was below 5%, and they were usually not isolated and characterized. It should be pointed out that the stereogenic center in the acetylene component can influence direction of asymmetric induction only if the nitrone is not chiral,[11b] or its stereogenic center is not located next to the C=N double bond.[11b] In the case of mismatched pairs, however, the configuration at the C-5 center of the carbapenam skeleton may also be affected by the configuration of the stereogenic center in the acetylene portion leading to the increased content of the *trans* isomers.

The results of the first series of experiments are collected in Table 1. As can be seen, removal of any structural element from dioxolane ring in **2**, results in an apparent decrease of the acetylenes' reactivity. Comparison of the results for acetylene **6** with those obtained for **7** and **8** indicates that the presence of two geminal methyl groups is also important for reactivity of the dipolarophile. The lower yields for **7** and **8** can be attributed to the increased degree of freedom of the acetal chain. Based on these observations it seems reasonable to conclude that acetylenes' oxygen atoms play crucial role on acetylenes' reactivity. It can be assume that one or both

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TABLE 1. Results of Reactions of 1 with Acetylenes 2 and 6−8

Amount of CuI [mol%]	Time [h]	Yields [%]			
		2	6	7	8
100	24	94	75	41	40
100	2	80	46	n.d.	n.d.
5	24	78	30	n.d.	n.d.

n.d.= to low to be determined.

TABLE 2. Results of Reactions of 1 with Acetylenes 2, 9, 12 and 13

Amount of CuI [mol%]	Time [h]	Yields [%]			
		2	9	12	13
100	24	94 (60[a])	64 (80[a])	55 (52[a])	56 (30[a])
100	2	80 (47[a])	36 (49[a])	55	57
5	24	78	54 (72[b])	35 (36[b])	49 (31[b])
5	2	80	33 (37[b])	36	31

[a]In the presence of 1,10-phenantroline (100 mol %). [b]In the presence of 1,10-phenantroline (5 mol %).

oxygen atoms plausible coordinate to copper ion and, as a consequence, a mutual orientation of oxygen atoms lone pairs is crucial for such complexation. It may be presumed that both methyl groups stabilize conformation of compound **2** and to some extend stabilize conformation of compound **6**, which consequently makes copper coordination by these acetylenes more effective.

For the next series of experiments we selected acetylenes **9**, **12**, **13** and their reactivity was compared to that of the acetylene **2** (Table 2). Reactions of **9**, **12** and **13** with the nitrone **1** provided the corresponding carbapenams **17**, **20** and **21**, respectively.

As can be seen from Table 2, the replacement of dioxolane ring in **2** by two *O*-benzyl groups (acetylene **9**) resulted in a diminishing of the effectiveness of the Kinugasa reaction in both variants, stochiometric and catalytic, likely due to the same effects noticed for compounds **6**−**8**. An enlargement of the 5-membered dioxolane ring of **2** into 1,3-dioxane **12** or 1,4-dioxane system **13** caused similar effect, demonstrated by a lower reaction yield in both cases. Once again, it proves that dioxolane ring is optimal for the most effective coordination of the copper ion. For both dioxane acetylenes such interaction is disturbed by both the steric (lack of proper distance between oxygen and copper atoms) and conformational disorders.

As was described above, the acetylene **2** is more reactive then compound **3**, suggesting that the dioxolane system offers better coordination of copper(I) ion than the 1,2-acetal. Results collected in Table 3, indicate additionally that a presence of two oxygen atoms is critical and optimal for the effective coordination of the copper ion and thus to improve the activation of the triple bond. For any other case (like **10** or **11**), the reactions gave lower yields under standardized reaction conditions.

The copper(I) complexes with terminal acetylenes are usually highly aggregated species, engaging in a range of

TABLE 3. Results of Reactions of 1 with Acetylenes 3, 10, and 11

Amount of CuI [mol%]	Time [h]	Yields [%]		
		10	3	11
100	24	45 (55[a])	72 (94[a])	31 (36[a])
100	2	12	62 (68[a])	10
5	24	n.d.	58 (97[b])	n.d.
5	2	n.d.	60[b]	n.d.

[a]In the presence of 1,10-phenantroline (100 mol %). [b]In the presence of 1,10-phenantroline (5 mol %); n.d. = to low to be determined.

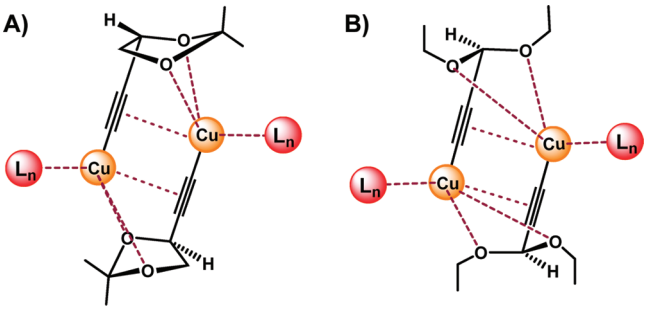

FIGURE 2. Plausible coordination of copper(I) ion by acetylene molecules **2** and **3**. The L_n refers to all nucleophilic ligands or reagents involved in the coordination sphere of the copper ion (i.e., nitrones' oxygen atom, halogen atom, 1,10-phenatroline, triethylamine, acetonitrile).

σ- and π-interactions.[25−27] Although the precise nature of the reactive alkynyl copper species is still not well-known, some recent experimental and computational results reveal that dinuclear copper(I) acetylides display enhanced reactivity in 1,3-dipolar cycloaddition reactions (e.g., copper-mediated azide-alkene cycloaddition).[28,29]

On the basis of that, we assumed that the observed enhancement of reaction rate for acetylenes **2** and **3** may result from the formation of a highly reactive, rigid dinuclear copper(I) complexes as shown in Figure 2. In the case of **2**, each copper ion coordinates to both dioxolane ring oxygen atoms and both triple bonds (Figure 2A). Remaining free sites within the copper coordination space are occupied by the nitrone. Additional participation of solvent or base molecules as ligands[30] cannot be excluded. The rigid structure of dioxolane ring stabilizes its conformation and enables the effective interaction of oxygen atoms with copper ion. Such coordination is less effective in the case of acetylenes **6**−**9** due to the increased degree of freedom of their more flexible structures. The crucial conformation regime, necessary for the effective coordination of copper Cu(I) ion is confirmed also by further experiments

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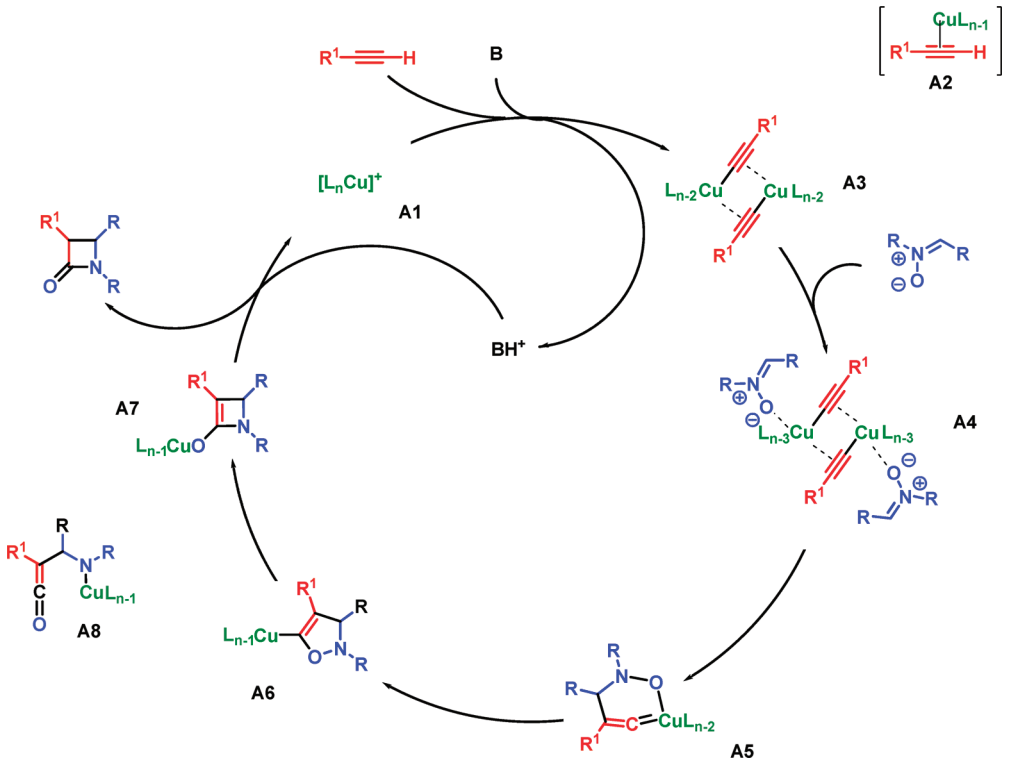
(30) During the investigation of the reaction between **1** and phenyl acetylene, we found that the best yields (70−80%) were achieved when 4 equiv of a base (e.g., Et_3N) with respect to copper salt were applied (when the ratio was 1:1, the yields were ca. 50%), which indicates that amine bases can also participate in coordination of cooper ion (not only MeCN used as a solvent).

SCHEME 4. Proposed Catalytic Cycle for Investigated Kinugasa Cascade Process[a]



[a] L_n refers to all nucleophilic ligands involved in the coordination sphere of the copper ion (i.e., halogen atom, oxygen atoms of the acetylene moiety, 1,10-phenatroline, triethylamine, acetonitrile).

with acetylenes bearing more flexible 1,3- or 1,4-dioxane ring (**12** and **13**).

The similar interaction as seen for **2**, can be assumed for acetylene **3** (Figure 2B). However, the larger distance between one oxygen atom and copper ion causes such complexation to be less effective. In the case of the latter acetylene, this is reflected in a lower reaction yield. It should be underlined that despite of many efforts we were not able to obtained crystal of copper acetylide complexes to confirm our assumption by X-ray methods.

It is interesting to compare the influence of 1,10-phenantroline addition. The significant increase of the reaction yield in the case of acetylene **3** may indicate synergistic effect of both oxygen atoms and *N*,*N*-ligand. In contrast, the addition of phenantroline ligand to the reaction of nitrone **1** with acetylene **10** causes only a slight enhancement of the yield. On the other hand, the opposite effect of 1,10-phenantroline in the case of **2** could potentially be explained assuming interference with the 1,3-dioxolane ring effect, probably due to the competitive complexation of the metal ion. A similar situation (competitive complexation of $[Cu^+]$) can occur if additional oxygen atoms of the ethoxy group (**11**), or two methoxy groups (**13**) are introduced to the acetylene molecule. Such result again confirms the critical role of oxygen atoms and their location in the acetylene molecule.

The positive effect of the addition of 1,10-phenantroline was also noticed for acetylene **9** (see Table 2). In this case, greater degree of freedom of the benzylated 1,2-diol unit in comparison to the acetylene **2** decreases the effective copper ion coordination. The plausible cocoordination of the copper ion by 1,10-phenantroline leads to increase of the reaction yield in both stochiometric and catalytic variant. However, acetylene **9**, even supported by 1,10-phenantroline, is still less reactive than **2** and even than **3** (compare the results after 2 h reaction time).

TABLE 4. Results of Reactions of Nitrones 1 and *ent*-1 with Acetylenes 23a and 23b (Scheme 6)

nitrone	acetylene	CuI [mol %]	time [h]	yield [%]	*cis*/*trans*[a]
1	**23a**	100	22	65	70:30
***ent*-1**	**23a**	100	20	75	> 95: < 5
1	**23b**	100	24	52	90:10
***ent* -1**	**23b**	100	24	54	> 95: < 5
1	**23a**	5	24	79	70:30
***ent* -1**	**23a**	5	21	80	> 95: < 5
***ent* -1**	**23a**	5	2	68	> 95: < 5

[a] Determined by ^{1}H NMR.

Owing to the high rate and excellent yield of both reactions involving acetylenes **2** and **3** with nitrone **1** we decided to investigate their catalytic variant in presence of 5 mol % of CuI (with or without the aid of 1,10-phenantroline). We found that reactions, which under standard conditions proceeded in a good yield (i.e., >70%), in the presence of catalytic amount of copper ion (5 mol %) offer acceptable yields (Tables 2–4). For other, previously investigated simple acetylenes,[11] the reaction yields are low, or very low, under catalytic reaction conditions after 24 h.

Based on our observations, as well as other reported cases of copper-mediated acetylene-azide cycloaddition,[15a,29,31] we proposed the plausible catalytic cycle for investigated cascade process (Scheme 4). Sequence begins with the

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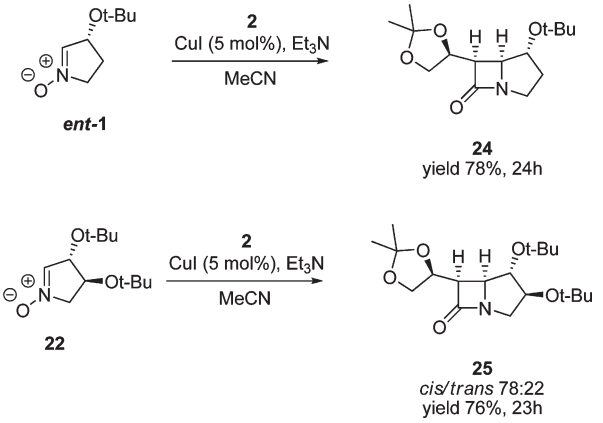
SCHEME 5. Reactions of Nitrones *ent*-1 and 22 with Acetylene 2



coordination of the alkyne to Cu(I) species **A1** to form π-complex **A2** in which the copper ion is also linked to other nucleophilic centers (oxygen atom/atoms, phenyl ring). The deprotonation of **A2** leads to the dinuclear copper(I) complex **A3** that, in the presence of nitrone, undergoes stepwise or concerted cycloaddition leading to **A6**. In case of stepwise process, which should be more plausible in case of the metal-catalyzed reaction, it may proceed through intermediates **A4** and **A5**, in analogy to the mechanism of copper-mediated reaction of azides with acetylenes proposed by Sharpless.[15a] Then, six-membered copper metallocycle **A5** contracts to five-membered isoxazoline **A6** and rearranges to enolate **A7**. Finally, protonation of **A7** gives the desired 2-azetidinone and releases the copper catalyst to a catalytic cycle.

Not much is known about the course of the rearrangement process. The most plausible path, proposed by Tang,[12c] assumes formation of ketene **A8** as an intermediate. Such an assumption seems to be correct in light of the recent Shimizu's investigation[32] related to cyclization of aminoketenes to 2-azetidinone. The much older mechanism, proposed by Ding and Irwin,[9a] which assumes that rearrangement proceeds through bicyclic oxaziridinium salt, seems to be less plausible.

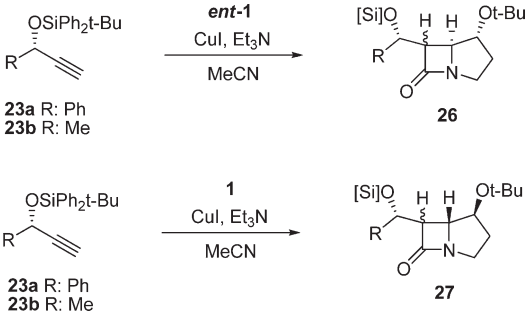
The possibility to efficiently carry out the Kinugasa reaction involving cyclic nitrones in the presence of catalytic amounts of copper salts prompted us to investigate other chiral acetylenes and other nitrones. We selected mismatched pairs **2** with nitrone ***ent*-1** or nitrone **22**, readily available from tartaric acid (Scheme 5). In both cases, reactions led to the desired carbapenams in a yield better than 75%.

Interesting results were obtained for reactions involving acetylenes **23a** and **23b** (Scheme 6). As we shown recently,[11b] the reactions of the latter one with nitrones **1** and ***ent*-1** proceed in moderated yields, while the analogues processes involving the former one give significantly better yields, around 70% (Table 4).

The observed better result for acetylene **23a** led us to a conclusion that the 1,3-dioxolane (or 1,2-acetal) moiety bound to the triple bond is likely not the only efficient activator for the Kinugasa process. Consequently, it can be assumed that any alkyne substituent can be a good activator

(32) Hachiya, I.; Yoshitomi, T.; Yamaguchi, Y.; Shimizu, M. *Org. Lett.* **2009**, *11*, 3266.

SCHEME 6. Reactions of Nitrones 1 and *ent*-1 with Acetylenes 23a and 23b (for Yields see Table 4)



of the reaction providing that it contains other functionality that is able to efficiently coordinate copper ion and destroy copper acetylide aggregates to afford a highly reactive dinuclear copper complex.

Such a conclusion sheds more light on our previous experimental observations by providing additional evidence in support of the above assumptions. For example, when nonfunctionalized alkynes (e.g., heptyne or hexyne) or linear alkoxyacetylenes (e.g., ethoxyethyne or phenoxyethyne) were applied no reaction was observed; in those cases the lack of proper functionality that is able to decompose the acetylides' aggregates, disables their efficient 1,3-dipolar cycloaddition and effective transformation to 2-azetidinone derivatives.

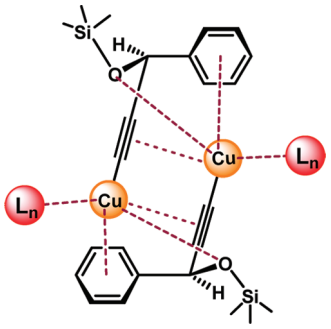


FIGURE 3. Plausible coordination of copper(I) ion by acetylene **23a**. The L_n refers to all nucleophilic ligands or reagents involved in the coordination sphere of the copper ion (i.e., nitrones' oxygen atom, halogen atom, 1,10-phenatroline, triethylamine, acetonitrile).

The enhanced reactivity of **23a** can be plausibly explained by the stereoelectronic effects (Figure 3). The bulky silyl protection group adopts an optimal orientation to minimize steric interactions and causes better complexation of the copper ion by the oxygen atom which is more nucleophilic owing to the O−Si bond effect. The observed lower yield of reactions with **23b** bearing a terminal methyl group instead of the phenyl ring (**23a**) indicates that the latter one is a crucial structural element for an enhancement of the reactivity (*via* interaction of aromatic sextet with the copper ion, Figure 3).

Conclusions

The enhancement of the Kinugasa reaction rate for acetylenes derived from glyceraldehyde and propargyl aldehyde

is probably the result of formation of the highly reactive rigid dinuclear copper(I) complex in which each copper ion is coordinated to one or both oxygen atoms in the acetylene molecule and to both triple bonds. The rigid structure of the dioxolane ring stabilizes the conformation of the acetylide and enables an optimal interaction of oxygen atoms with the copper ion. Such complexation is less effective in the case of more flexible structures. It has been demonstrated that a phenyl ring may replace one of the oxygen atoms to provide coordination of the copper ion by the aromatic sextet. However, two nucleophilic centers are necessary for the effective coordination of the copper ion and thus to activate a triple bond for the cycloaddition reaction with nitrones. Kinugasa reactions involving highly active acetylenes, which were found to proceed in a high yield under standard conditions, can also be performed in the presence of a catalytic amount of the copper salt to provide products in an acceptable yield without any decrease of diastereoselectivity. Lower activity of the acetylene consequently requires prolongation of the reaction time, which promotes side processes; therefore, the yield is lower and the reaction can not be performed effectively in the presence of catalytic amounts of the copper salt.

Experimental Procedures

Synthesis of β-Lactams *via* Kinugasa Reaction. General Procedure. To a suspension of CuI (0.5 mmol, 95 mg) in dry, degassed MeCN (3 mL) was added 280 μL (2.0 mmol) of triethylamine (and additives like 1,10-phenantroline, 0.5 mmol, 90 mg). After cooling to 0 °C, a solution of acetylene (0.5 mmol) in 1 mL of MeCN was added, and the obtained mixture was stirred for 15 min. Subsequently, a solution of nitrone (1 mmol) in MeCN (1−2 mL) was added slowly, and the mixture was kept at 0 °C for additional 15 min. After that time, the cooling bath was removed and the reaction mixture was stirred at room temperature under nitrogen atmosphere. The progress of the reaction was monitored by TLC. Subsequently, the solvent was removed under diminished pressure and the residue was purified by column chromatography on silica gel or florisil. The diastereoisomers' ratio was assigned by ^{1}H NMR.

Spectral data of compounds **4**, **5a**, **5b**, and **24**−**27** can be found in our previous reports.[11] For atom numbering, see Scheme 2.

Compound 14. Colorless oil; $[\alpha]_D$ +127.6 (*c* 0.44, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) *δ*: 4.24 (1H, dt, *J* 6.7, 2.3 Hz, H-1), 3.65−3.60 (2H, m, H-5, H-6), 3.57 (1H, dd, *J* 10.5, 4.5 Hz, CH*H*O), 3.48 (1H, dd, *J* 10.5, 7.7 Hz, C*H*HO), 3.37−3.34 (1H, m, H-3), 3.10 (3H, s, MeO), 2.80 (1H, ddd, *J* 11.6, 9.6, 6.6 Hz, H-3′), 1.88−1.82 (1H, dddd, 13.1, 9.5, 8.0, 6.8 Hz, H-2), 1.70−1.58 (1H, m, H-2′), 1.20 (3H, s, Me), 1.17 (3H, s, Me), 1.08 (9H, s, *t*-Bu). ^{13}C NMR (125 MHz, C_6D_6) *δ*: 177.5, 100.1, 73.7, 70.8, 63.9, 56.2, 52.4, 48.6, 45.5, 39.5, 28.4, 24.3; IR (film) 1767 cm^{-1}. Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 63.10; H, 9.56; N, 4.89. HR MS (ESI) Calcd for $C_{15}H_{27}NO_4Na$ [M + Na$^+$]: 308.1832. Found: 308.1833.

Compound 15. Colorless oil; $[\alpha]_D$ +53.5 (*c* 0.45, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) *δ*: 4.37 (1H, d, *J* 6.4 Hz, O−CH*H*-O); 4.34 (1H, d, *J* 6.4 Hz, O−C*H*H−O) 4.13 (1H, dt, *J* 6.3, 2.9 Hz), 3.61 (1H, dd, *J* 10.9, 4.5 Hz, CH*H*O), 3.59−3.55 (2H, m, H-5, H-6), 3.52 (1H, dd, *J* 10.9, 8.0 Hz, C*H*HO), 3.38−3.34 (1H, m, H-3), 3.13 (3H, s, Me), 2.76 (1H, ddd, *J* 11.6, 9.1, 6.8 Hz, H-3′), 1.78 (1H, dddd, *J* 13.1, 8.9, 8.0, 6.7 Hz, H-2), 1.62 (1H, ddt, *J* 13.1, 6.7, 2.2 Hz, H-2′), 1.02 (9H, s, *t*-Bu); ^{13}C NMR (125 MHz, C_6D_6) *δ*: 176.7, 96.2, 73.4, 70.3, 63.0, 62.5, 54.8, 51.9, 44.9, 39.0, 28.0; IR (film) 1767, 1112 cm^{-1}. Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.64; H, 8.98; N, 5.45. HR MS (ESI) Calcd for $C_{13}H_{23}NO_4Na$ [M + Na$^+$]: 280.1519. Found: 280.1516.

Compound 16. The mixture of diastereoisomers in ratio 1:1. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 4.45 (1H, q, *J* 5.3 Hz), 4.37 (1H, q, *J* 5.3 Hz), 4.30 (2H, m), 3.73 (1H, dd, *J* 10.7, 3.8 Hz); 3.67−3.58 (3H, m), 3.54−3.32 (4H, m), 3.30−3.20 (2H, m), 2.84−2.74 (2H, m), 1.95−1.87 (1H, m), 1.85−1.75 (1H, m), 1.70−1.63 (2H, m), 1.54−1.45 (2H, m), 1.39−1.32 (2H, m), 1.18−1.15 (6H, 2 × d, *J* 5.3 Hz), 1.12 (9H, s, t-Bu), 1.10 (9H, s, t-Bu), 0.90−0.83 (6H, 2x t, *J* 7.4 Hz). IR (film) 1768 cm^{-1}. HR MS (ESI) Calcd for $C_{15}H_{27}NO_4Na$ [M + Na$^+$]: 308.1832. Found: 308.1836.

Compound 17. Colorless oil; $[\alpha]_D$ −46.2 (*c* 0.85, CH_2Cl_2); ^{1}H NMR (600 MHz, C_6D_6) *δ*: 7.27−7.00 (10H, 2xPh), 4.64 (1H, d, *J* 11.3 Hz, C*H*HPh), 4.37 (1H, d, *J* 11.3 Hz, CH*H*Ph), 4.28 (1H, dt, *J* 6.2, 1.9 Hz, H-1), 4.27 (2H, s, CH_2Ph), 3.76 (1H, ddd, *J* 7.5, 5.7, 3.7 Hz, H-1′), 3.65 (1H, dd, *J* 10.2, 3.7 Hz, H-2′a), 3.62 (1H, dd, *J* 6.0, 1.9 Hz, H-6), 3.59 (1H, ddd, *J* 11.3, 7.9, 2.3 Hz, H-3a), 3.53 − 3.47 (2H, m, H-5, H-2′b), 2.77 − 2.71 (1H, m, H-3b), 1.72−1.65 (1H, m, H-2a), 1.50 (1H, ddt, *J* 12.8, 6.0, 2.2 Hz, H-2b), 0.93 (9H, s, *t*-Bu). ^{13}C NMR (151 MHz, C_6D_6, aromatic carbon atoms are omitted) *δ*: 177.8, 75.0, 73.4, 73.0, 72.2, 71.0, 70.8, 63.8, 53.5, 45.4, 39.1, 28.1. IR (film) v: 1760 cm^{-1}. Anal. Calcd for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85; N, 3.31. Found: C, 73.70; H, 7.82; N, 3.30. HRMS (ESI) Calcd for $C_{26}H_{33}NO_4Na$ [M + Na$^+$]: 446.2307. Found: 446.2312.

Compound 18. Colorless oil; $[\alpha]_D$ −132.5 (*c* 0.92, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 4.28 (1H, dt, *J* 6.9, 3.4 Hz), 3.70−3.62 (4H, m, H-3, H-5, H-6, CH*H*O), 3.56 (1H, dd, *J* 10.4, 8.0 Hz, C*H*HO), 3.38 (3H, s, Me) 2.96 (1H, dt, *J* 11.5, 7.6 Hz, H-3′), 2.14 (1H, dtd, *J* 13.2, 8.2, 7.1 Hz, H-2), 1.92 (1H, ddt, 13.2, 7.5, 3.9 Hz, H-2′), 1.21 (9H, s, *t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 177.5, 74.1, 70.0, 67.5, 62.7, 58.9, 51.4, 44.6, 39.2, 28.3. IR (film) 1765 cm^{-1}. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.39; H, 9.33; N, 6.14. HR MS (ESI) Calcd for $C_{12}H_{21}NO_3Na$ [M + Na$^+$]: 250.1414. Found: 250.1409.

Compound 19. Colorless oil; $[\alpha]_D$ −21.7 (*c* 1.6, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) *δ*: 4.70 (1H, d, *J* 6.1 Hz, H-1), 3.77 (1H, ddd, *J* 11.6, 8.0, 1.3 Hz, H-3a), 3.70−3.62 (8H, m,OCH_2CH$_3$, H-5, H-6), 2.89 (1H, ddd, *J* 11.6, 11.3, 6.0 Hz, H-3b), 2.20−2.13 (1H, m, H-2a), 1.66−1.62 (1H, m, H-2b), 1.11 (9H, s, *t*-Bu), 1.09−1.07 (9H, m, 3× OCH$_2$CH_3); ^{13}C NMR (125 MHz, C_6D_6) *δ*: 175.2, 112.3, 96.4, 73.5, 63.3, 58.4, 58.2, 46.5, 38.5, 28.6, 15.5; IR (film) 1771 cm^{-1}. Anal. Calcd for $C_{17}H_{31}NO_5$: C, 61.98; H, 9.48; N, 4.25. Found: C, 62.00; H, 9.50; N, 4.24. HR MS (ESI) Calcd for $C_{17}H_{31}NO_5Na$ [M + Na$^+$]: 352.2094. Found: 352.2095.

Compound 20. Colorless oil; $[\alpha]_D$ −71.7 (*c* 0.63, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 4.26 (1H, br d, *J* 6.2 Hz, H-1), 3.73 (1H, ddd, *J* 11.2, 9.8, 2.8 Hz, H-1′), 3.63 (1H, ddd, *J* 11.5, 7.7, 1.1 Hz, H-3a), 3.60 (1H, br d, *J* 5.9 Hz, H-6), 3.57−3.49 (2H, m, H-3′a/b), 3.19 (1H, dd, *J* 9.5, 5.9 Hz, H-5), 2.81 (1H, td, *J* 11.5, 5.9 Hz, H-3b), 1.75−1.48 (4H, H-2a/b, H-2′a/b), 1.39 (3H, s, Me), 1.23 (3H, s, Me), 1.11 (9H, s, *t*-Bu); ^{13}C NMR (151 MHz, C_6D_6) *δ*: 177.0, 97.9, 73.6, 70.3, 65.4, 63.7, 59.0, 57.1, 45.7, 39.4, 30.2, 29.6, 28.0, 18.7; IR (film) 1765 cm^{-1}. Anal. Calcd for $C_{16}H_{27}NO_4$: C, 64.42; H, 9.15; N, 4.71. Found: C, 64.39; H, 9.16; N, 4.69. HR MS (ESI) Calcd for $C_{16}H_{27}NO_4Na$ [M + Na$^+$]: 320.1832. Found: 320.1863.

Compound 21. Colorless oil; $[\alpha]_D$ −188.7 (*c* 0.53, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 4.77 (1H, br d, *J* 5.8 Hz, H-1), 4.22 (1H, ddd, *J* 11.6, 4.9, 3.4 Hz, H-1′), 3.80−3.75 (2H, dd, *J* 11.8, 7.8 Hz, for H-3 and t, *J* 11.6, 11.3 Hz, for H-2′a) 3.68 (1H, br d, *J* 5.8 Hz, H-6), 3.51 (1H, dd, *J* 11.3, 3.4 Hz, H-2′b), 3.43 (1H, dd, *J* 5.8, 4.9 Hz, H-5), 3.31 (3H, s, MeO), 3.29 (3H, s, MeO), 2.89

(1H, m, H-3′), 2.09 (1H, m, H-2), 1.78 (1H, dd, *J* 12.8, 5.5 Hz, H-2′), 1.30 (3H, s, Me), 1.25 (3H, s, Me), 1.24 (9H, s, *t*-Bu). ^{13}C NMR (125 MHz, C_6D_6) δ: 177.5, 99.2, 98.4, 96.5, 73.6, 71.3, 65.0, 64.6, 60.9, 53.0, 48.1, 47.9, 39.5, 28.4, 17.7, 17.6. IR (film) 1767 cm^{-1}. Anal. Calcd for $C_{18}H_{31}NO_6$: C, 60.48; H, 8.74; N, 3.92. Found: C, 60.50; H, 8.75; N, 3.90. HR MS (ESI) Calcd for $C_{18}H_{31}NO_6Na$ [M + Na$^+$]: 380.2044. Found: 380.2054.

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Supporting Information Available: Experimental procedures for acetylenes **2**, **6**−**13** and their spectral and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.