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# Enantioselective concomitant creation of vicinal quaternary stereogenic centers via cyclization of alkynols triggered addition of azlactones

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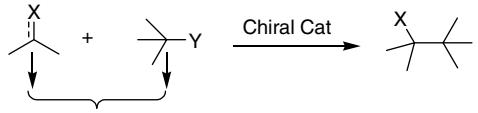
ABSTRACT

An asymmetric cyclization of alkynols triggered addition of azlactones catalyzed by a combined catalyst system consisting of a chiral gold phosphate and a phosphoric acid produces conformationally restricted amino acid precursors bearing vicinal quaternary stereogenic centers in high levels of stereoselectivity.



The enantioselective construction of quaternary stereogenic centers has long been holding great importance, but accepted as a challenging task in organic synthesis. As a result, great efforts have been made in this field, leading to elegant advances on the enantioselective formation of the single quaternary stereogenic carbon and of adjacent quaternary and tertiary stereogenic centers.[1] Unarguably, the concomitant creation of the vicinal quaternary stereogenic centers in highly enantioselective manner is an even more formidable challenge owing to the huge steric repulsion between the two tetrasubstituted carbons. So far, very few successful methods have been available to forge the skeletons of this type, including intramolecular double Heck reaction, aldol reaction, [3+2] cycloaddition, and others.[2] All these reactions involve substrates with pre-quaternary carbon centers where the reactions take place (Eq. 1). Herein, we propose an alternative strategy, which consists of a conversion of a linear functionality, carbon–carbon triple-bond, to an electrophile with a pre-quaternary carbon center able to subsequently undergo an addition reaction, to enantioselectively afford vicinal quaternary stereogenic centers (Eq. 2). As proof-of-principle, we will present a highly enantioselective intramolecular cyclization of alkynols triggered addition reaction of azlactones catalyzed by a combined catalyst system of a gold complex and a chiral Brønsted acid.

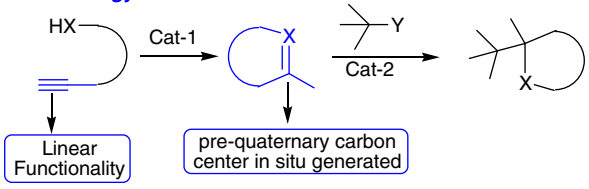
***Previous Strategy for Concomitant Creation of Vicinal Quaternary Stereogenic Centers***




(1)

pre-quaternary carbon centers: X = C (Heck and 3+2),
O (aldol, alkylation)
Y = Proton or leaving group

***This Strategy***




(2)

Alkynols of type **1** under the catalysis of π-Lewis acids undergo an intramolecular hydroxylation to give enol ethers, which proved to be reactive toward nucleophiles, providing a robust platform for the creation of a variety of important transformations,[3] whereas no enantioselective variants have been established, yet. Tepe, Terada, and co-workers have disclosed a Brønsted acid-catalyzed aldol reaction of vinyl ethers with azlactones, creating adjacent quaternary and tertiary stereogenic centers with excellent stereocontrol.[4] Recently, we and others have demonstrated the excellent compatibility of gold complexes and Brønsted acids in catalysis.[5] These achievements prompted us to speculate about the possibility to

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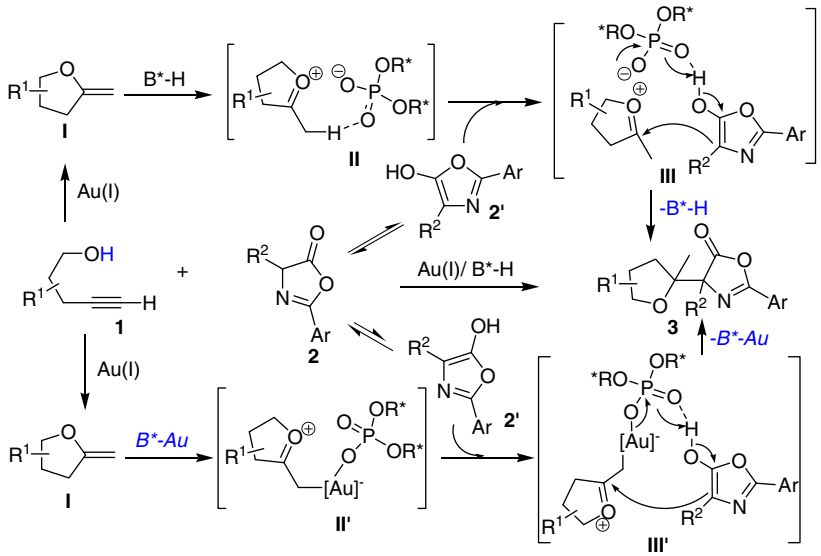
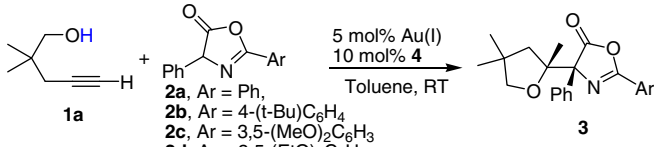


**Scheme 1.** The possibility to initiate the titled reaction.

initiate a cyclization of alkynols triggered addition of azlactones by using a combined catalyst system consisting of a chiral phosphoric acid[6] and a gold complex for the concomitant creation of vicinal quaternary stereocenters (Scheme 1). This proposed enantioselective protocol presumably proceeds initially with an intramolecular hydroalkoxylation with a suitable gold catalyst to generate an enol ether **I**. Theoretically, the enol ether **I** participates in the addition reaction of the azlactone through two possible intermediates including (1) an ion pair of a chiral conjugate base and an oxonium ion **II** formed from protonation of the enol ether with Brønsted acid **4** and (2) a chiral oxonium intermediate **II′** generated from coordination of the chiral gold catalyst to the double bond of the enol ether.[3a,b,7] Either the intermediate **II**[4] or **II′**[8] is principally able to participate in the enantioselective addition of the azlactones via the transition state **III** or **III′**, furnishing the products **3**, which can be readily transformed into a new type of amino acids potentially useful in the construction of conformationally constraint peptides for the medicinal purpose.[9]

The implementation of our hypothesis began with a reaction of 2,2-dimethyl-4-pentynol (**1a**) with 2,4-diphenyloxazol-5(4*H*)-one (**2a**) in the presence of 10 mol % of phosphoric acid **4** and 5 mol % of (Ph$_3$P)AuMe (Fig. 1).[5a] Encouragingly, the reaction proceeded smoothly in toluene at room temperature to give the desired product **3a** in 95% yield, but with moderate diastereo- and enantioselectivities (Table 1, entry 1). The variation of substitution pattern at C4 of the azlactone found that enlarging the substituent was beneficial to the stereoslectivity while the reactivity was maintained (entries 2–5). As a consequence, the use of the azlactone **2e** provided the highest stereoselectivity (entry 5, 80/20 dr, 91% ee). With the optimal azlactone substrate **2e** in hand, we then evaluated the gold complexes. Basically, the variation of the phosphine ligands[10] had very little influence on the stereoselectivity (entries 6–8), but

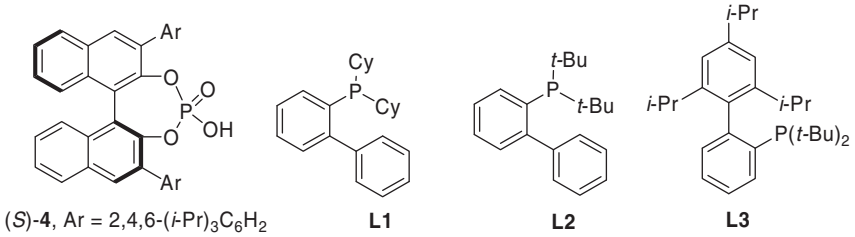
**Table 1**
Identification of optimal gold catalyst and azlactone[a]



**1a** + **2a**, Ar = Ph, **2b**, Ar = 4-(t-Bu)C$_6$H$_4$, **2c**, Ar = 3,5-(MeO)$_2$C$_6$H$_3$, **2d**, Ar = 3,5-(EtO)$_2$C$_6$H$_3$, **2e**, Ar =3,4,5-(MeO)$_3$C$_6$H$_3$ → 5 mol% Au(I), 10 mol% **4**, Toluene, RT → **3**

| Entry | Ar (**2**) | Au(I) | Yield (%)[b] | dr[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | **2a** | (Ph$_3$P)AuMe | 95 | 67/33 | 63 (36) |
| 2 | **2b** | (Ph$_3$P)AuMe | 93 | 68/32 | 69 (30) |
| 3 | **2c** | (Ph$_3$P)AuMe | 60 | 67/33 | 50 (35) |
| 4 | **2d** | (Ph$_3$P)AuMe | 91 | 72/28 | 68 (26) |
| 5 | **2e** | (Ph$_3$P)AuMe | 88 | 80/20 | 91 (37) |
| 6 | **2e** | L1AuMe | 91 | 81/19 | 90 (34) |
| 7 | **2e** | L2AuMe | 94 | 80/20 | 91(30) |
| 8 | **2e** | L3AuMe | 91 | 80/20 | 92 (35) |
| 9 | **2e** | (Ph$_3$P)AuNTf$_2$ | 95 | 63/37 | 16 (45) |
| 10 | **2e** | (Ph$_3$P)AuOBz | 93 | 78/22 | 89 (34) |
| 11 | **2e** | L3AuMe | 96 | 84/16 | 95 (33)[e] |
| 12 | **2e** | L3AuMe | 99 | 85/15 | 95 (31)[e,f] |
| 13 | **2e** | L3AuMe | 86 | 84/16 | 93 (24)[g] |
| 14 | **2e** | L3AuMe | 99 | 84/16 | 94 (29)[h] |

[a] The reaction of **1a** (0.2 mmol) and **2** (0.1 mmol) was carried out with 3 Å MS (100 mg) in toluene (1 mL) for 15 h.
[b] Isolated yield.
[c] Determined by $^1$H NMR.
[d] Determined by HPLC and the ee values in parenthesis are observed for minor diastereomer.
[e] The reaction was conducted at 0 °C for 48 h.
[f] 3 Å MS (50 mg) and toluene (2 mL) were used.
[g] 5 mol % of **4** is used.
[h] 15 mol % of **4** was used.



(*S*)-**4**, Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$ **L1** **L2** **L3**

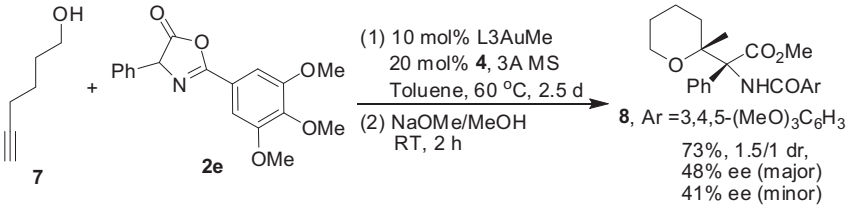
**Figure 1.** The organocatalyst and ligands used in this study.

the gold complex with a sterically bulky phosphine **L3**[11] offered the best results in terms of enantioselectivity (entry 8). In contrast, the counter anion exerted great impact on the reaction (entries 9 and 10). Although a high conversion was observed with the highly cationic $(Ph_3P)AuNTf_2$,[12] the stereoselectivity dropped dramatically (entry 9), presumably because $(Ph_3P)AuNTf_2$ offered a non-enantioselective background reaction to compete with phosphoric acid-catalyzed variant. Interestingly, less cationic $(Ph_3P)AuOBz$ proved to be a good partner of **4**, providing a high stereoselectivity (entry 10), probably because the $(Ph_3P)AuOBz$ reacted with **4** to generate a gold phosphate as $(Ph_3P)AuMe$ did.[5c] The screening of solvents revealed that non-polar solvents such as toluene and benzene were suitable reaction media (see Table S1, Supplementary data). Delightfully, the stereoselectivity could be further enhanced by lowering the temperature and concentration (entries 11 and 12, 95% ee). Tuning the stoichiometry of **4** to the gold complex revealed that an equimolar amount of phosphoric acid still rendered a smooth reaction albeit in a lower yield and slightly eroded ee (entry 13 vs 14), indicating that the chiral gold phosphate was capable of effectively catalyzing the addition reaction.

As the gold phosphate proved to be an efficient catalyst for the cascade reaction (Table 1, entry 13), we investigated the kinetic profile of the cascade reaction of **1a** with **2e** under the promotion of the combined catalyst with varying ratios of **4** to L3AuMe, to clarify if it was necessary to use excess amounts of phosphoric acid. As shown in Figure 2, when the second-order kinetic was applied, the plot of Ln([**3e**]/[**2e**] + 2) against time gave a linear relationship, from which rate coefficient could be determined, respectively, from the slope of the plot. The analysis of the plot indicated that the cationic gold phosphate[5c] generated from L3AuMe and **4** served as a good catalyst for the cascade reaction. However, the presence of excess amounts of phosphoric acid **4** significantly speeded up the reaction, in addition to offering a slightly higher ee (entry 12 vs 13, Table 1). The fact that the combination of 5 mol % L3AuMe and 10 mol % phosphoric acid **4** provided a faster reaction than 10 mol % of gold phosphate by a factor of 1.8 led to the conclusion that the phosphoric acid afforded a faster addition reaction of azlactone to enol ether than its gold salt. Moreover, these results also suggested that both the intermediates **II** and **II′** were involved in the asymmetric nucleophilic addition of azlactone to the enol ether. In addition, a control reaction between enol ether **5** and the azlactone **2e** proceeded smoothly to give **6** in similar yields and stereoselectivities in the presence of 5 mol % of either gold phosphate or **4** (Eq. 3). These results strongly supported that the addition reaction occurred via intermediates **II** and **II′**.

Having established the optimal conditions, we explored the generality for the substrates (Table 2). In addition to **1a**, 2,2-disubstituted 4-pentynols reacted cleanly with the azlactone **2e** to generate aldol-like products **3f**–**3h** with vicinal quaternary stereogenic centers in high levels of enantioselectivity for the major diastereomers (90–95% ee). 4-Bromophenyl substituted azlactone **2f** participated in a smooth cyclization triggered addition reaction with 2,2-disubstituted 4-pentynols to furnish the desired products **3i**–**3k** in high yields and high enantioselectivities (up to 86% ee). The *meta*-methylphenyl substituted azlactone **2g** underwent clean reactions with 2,2-disubstituted 4-pentynol, giving rise to a cyclic product **3l** with a moderate enantioselectivity (78% ee). The highly electronically rich 3,4-dimethoxyphenyl substituted azlactone **2h** could also be tolerated with a high enantioselectivity. The *para*-substitution of the aromatic ring with a highly electron-donating group enabled a highly enantioselective reaction to give products **3n**–**3q** in exquisite yields.

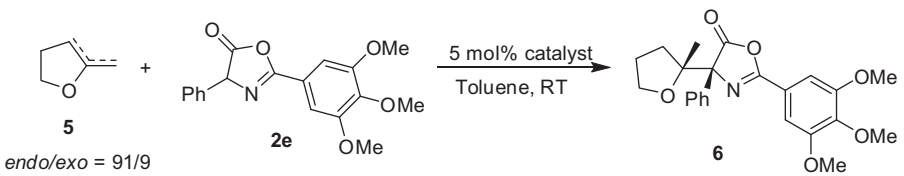
The further exploration of reaction generality revealed that 5-hexynol was much less reactive toward the azlactone **2e**. Thus, 5-hexynol **7** was unable to participate in the desired reaction under the optimal conditions. However, the reaction proceeded smoothly at 60 °C in the presence of 10 mol % of L3AuMe and 20 mol % of **4**, and after alcoholysis with sodium methoxide in methanol to furnish **8** in 73% yield (Eq. 4), albeit with unsatisfactory stereoselectivity (1.5/1dr, 48%, and 41% ee for the diastereomers, respectively).




(4)

Notably, a scale-up reaction of **2e** (1.0 g) with **1a** also proceeded smoothly to give the *syn*-**3e** in a high yield with slight erosion of the enantioselectivity (93% ee). The reduction of *syn*-**3e** with $LiAlH_4$ generated amido alcohol **9** in 84% yield. The Parikh–Doering oxidation[13] of **9** and followed by a condensation with benzenesulfonohydrazide furnished a hydrazone **10** (Scheme 2). The X-ray crystallography analysis of the optically pure **10** indicates that the configuration of *syn*-**3e** was assigned to be (*R*,*R*) (also see Supplementary data).

In summary, we have established an asymmetric cyclization of alkynols triggered addition of azlactones catalyzed by a combined catalyst system consisting of a chiral gold phosphate and a phosphoric acid, which results in a new strategy to convert the linear carbon–carbon triple bond functionality to a quaternary stereogenic center. This process provides a unique entry to access conformationally restricted amino acid precursors bearing vicinal quaternary stereogenic centers in high levels of stereoselectivity. In addition, this work first demonstrated that the chiral gold phosphate is able to catalyze highly enantioselective addition of




(3)

5 mol% L3AuMe+ 5 mol% **4**: 94%, 1.4/1 dr, 73(64%)ee
5 mol% **4**: 94%, 1.4/1 dr, 73(66%)ee

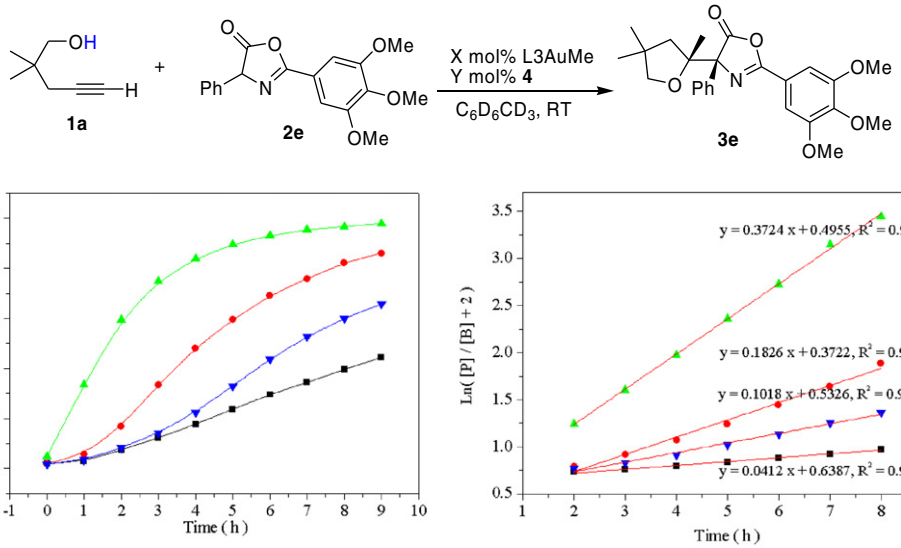
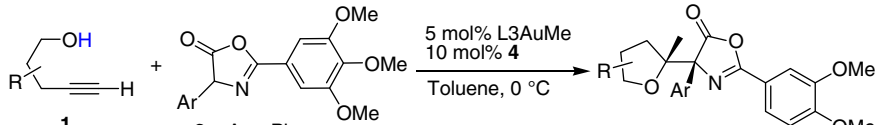
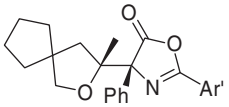



**Figure 2.** Kinetic studies on the cascade reaction of **1a** and **2e**: (■) the reaction catalyzed by 5 mol % L3AuMe and 5 mol % **4**; (●) the reaction catalyzed by 5 mol % L3AuMe and 10 mol % **4**; (▲) the reaction catalyzed by 5 mol % L3AuMe and 15 mol % **4**; (▼) the reaction catalyzed by 10 mol % L3AuMe and 10 mol % **4**. Two equivalents of ynol to azalactone **2e** were used for all these reactions. The reaction was monitored by $^1$H NMR at 10 °C.

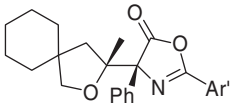
**Table 2**
Generality for the substrates[a,b,c,d]



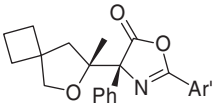

**2e**, Ar = Ph
**2f**, Ar = 4-Br$C_6H_4$
**2g**, Ar = 3-Me$C_6H_4$
**2h**, Ar = (3,4-MeO)$_2C_6H_3$
**2i**, Ar = 4-MeO$C_6H_4$



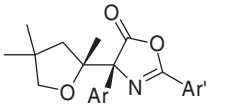
**3f**
98%, 87/13 dr, 95% (10%) ee



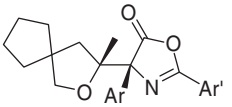
**3g**
98%, 87/13 dr, 90% (15%) ee



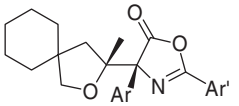
**3h**
96%, 86/14 dr, 93% (8%) ee



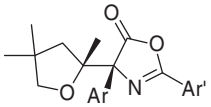
**3i**, Ar = 4-Br$C_6H_4$
75%, 78/22 dr, 80% (39%) ee



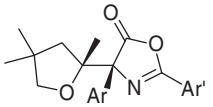
**3j**, Ar = 4-Br$C_6H_4$
90%, 86/14 dr, 86% (13%) ee



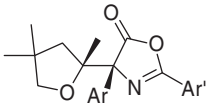
**3k**, Ar = 4-Br$C_6H_4$
88%, 81/19 dr, 81% (19%) ee



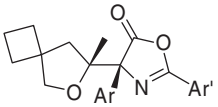
**3l**, Ar = 3-Me$C_6H_4$
78%, 81/19 dr, 78% (9%) ee
0 °C, 2.5 d



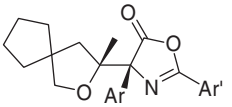
**3m**, Ar = 3,4-(MeO)$_2C_6H_3$
91%, 66/34 dr, 83% (15%) ee
0 °C, 3 d



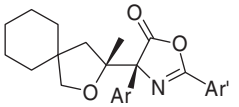
**3n**, Ar = 4-MeO$C_6H_4$
99%, 80/20 dr, 91% (27%) ee
0 °C, 2.5 d



**3o**, Ar = 4-MeO$C_6H_4$
95%, 83/17 dr, 90% (14%) ee
0 °C, 3 d

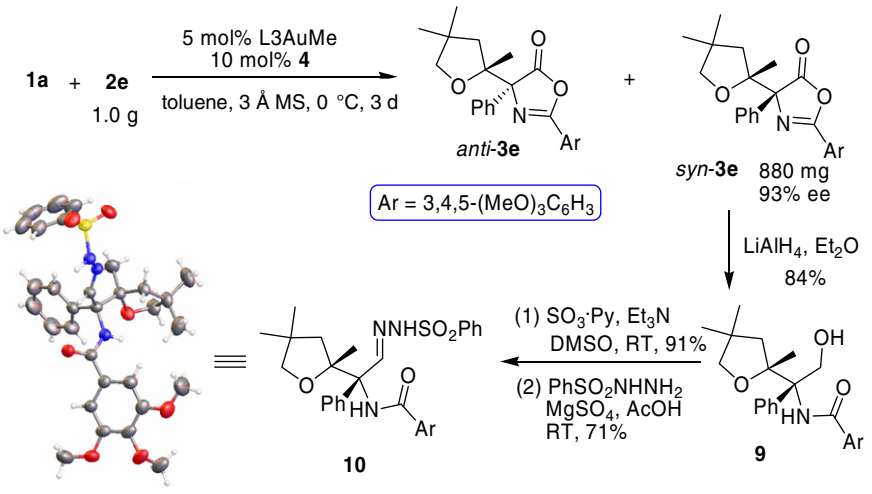


**3p**, Ar = 4-MeO$C_6H_4$
97%, 80/20 dr, 92% (5%) ee
0 °C, 3 d



**3q**, Ar = 4-MeO$C_6H_4$
94%, 82/18 dr, 90% (10%) ee
0 °C, 3 d

[a] The reaction of **1a** (0.2 mmol) and **2** (0.1 mmol) was carried out with 3 Å MS (100 mg) in toluene (1 mL) for 15 h.
[b] Isolated yield.
[c] Determined by $^1$H NMR.
[d] Determined by HPLC and the ee values in parenthesis are observed for minor diastereomers.




**Scheme 2.** Scale-up of the reaction and identification of the stereochemsitry of *syn*-**3e**.

azlactones to enol ethers by using chiral anion to control the stereochemistry.[8,14,15] Further investigations focused on the related transformations by using the binary catalyst system are underway.

## Acknowledgments

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## Supplementary data

Supplementary data (experimental details and characterization of new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.123.

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