Regioselectivity and diastereoselectivity of three-component reaction of \(\alpha\)-amino acid, dialkyl acetylenedicarboxylates and 2-arylidene-1,3-indanediones

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The 1,3-dipolar cycloaddition of active azomethine ylide, which were generated in situ from addition reaction of \(\alpha\)-amino acids with dialkyl acetylenedicarboxylates, with 2-arylidene-1,3-indanediones showed versatile regioselectivity and diastereoselectivity. The reaction of sarcosine and glycine afforded one kind of functionalized spiro[indene-2,3\(^\prime\)-pyrrolidines]. The other primary \(\alpha\)-amino acids such as alanine, phenylalanine and leucine gave another kind of regioisomeric spiro[indene-2,3\(^\prime\)-pyrrolidines]. The cyclic \(\alpha\)-amino acids resulted in the corresponding spiro[indene-2,2\(^\prime\)-pyrrolizines] and [indene-2,6\(^\prime\)-pyrrolo[1,2-c]thiazoles].

The tertiary amine such as pyridine, quinolone, isoquinoline promoted nucleophilic addition reaction of electron-deficient alkynes have attracted much research efforts in the past decades. Traditionally, the addition reaction of aromatic nitrogen-containing heterocycles such as pyridine, quinolone and isoquinoline to electron-deficient alkynes including dialkyl acetylenedicarboxylates resulted in active Huisgen 1,4-dipoles, which can be trapped by various reagents including dienophiles to accomplish diverse carbon–carbon bond formation reactions and various heterocyclic constructions (Fig. 1, eq. 1). In this decades, the similar active enamines derived from addition reaction of aromatic amines to electron-deficient alkynes were also widely recognized as useful synthons for the synthesis of various N- and O-heterocycles (Fig. 1, eq. 2). These kind of active enamines have the similar structural characters to that of the widely employed \(\beta\)-enamino and \(\beta\)-enmino esters and showed versatile applications in construction of nitrogen-containing heterocycles. Recently, we have found that the reaction of \(\alpha\)-amino acids with dialkyl acetylenedicarboxylates afforded a new kind of azomethine ylide, which could reacted with some typical dienophiles such as N-substituted maleimides and 3-methyleneoxindoles to give diverse pyrrolo[3,4-\(c\)]pyrrole and spiro[indoline-3,3\(^\prime\)-pyrrolidine] derivatives (Fig. 1, eq. 3). Comparing with the fruitful chemistry of active Huisgen 1,4-dipoles and the enarni esters, the reactivity of this kind of active 1,3-dipoles is still not broadly investigated. In order to develop the synthetic applications of this new kind azomethine ylides for diverse nitrogen-containing heterocyclic systems and continue our aim to explore more efficient and sustainable synthetic methodology for biologically important spiro compounds, herein we wish to report the interesting regioselectivity and diastereoselectivity of three-component reaction of \(\alpha\)-amino acids, dialkyl acetylenedicarboxylates and arylideneindane-1,3-diones.

Results and Discussions

According to our previously established reaction procedure for the 1,3-dipolar cycloaddition of azomethine ylides with maleimides or 3-phenacylideneoxindolines, the three-component reaction of \(\alpha\)-proline, dialkyl acetylenedicarboxylate and 2-arylidene-1,3-indanedione was carried out in ethanol at 50 °C for ten hours. After workup, the expected spiro[indene-2,2\(^\prime\)-pyrrolizines] \(1a-1f\) were predominately produced in 69–78% yields (Fig. 2, entries...
The similar reaction with thiazolidine-4-carboxylic acid also proceeded smoothly to give corresponding spiro [indene-2,6′-pyrrolo[1,2-c]thiazoles] 1g-1i in good yields (Fig. 2, entries 7–9). The structures of obtained spiro compounds 1a-1i were fully characterized by HRMS, IR, 1H and 13C NMR spectra. Because the obtained compounds have three chiral carbon atoms, several diastereoisomers might be formed in the reaction. We were...
pleased to find that only one diastereoisomer were predominately formed in the reaction by TLC monitoring and the spectroscopy. The single crystal structure of the spiro compound \(1g\) was determined by X-ray diffraction method (Fig. 3). It can be seen that the aryl group and the methoxycarbonyl group exist in cis-position of the newly-formed pyrrolidine ring. The methoxycarbonylmethyl group stands at trans-configuration. On the basis of the spectroscopy and single crystal structure, we could conclude that the spiro compounds \(1a-1i\) are all belonging to this kind of configuration and this 1,3-dipolar cycloaddition reaction showed very high disatereoselectivity.

Under same reaction conditions, sarcosine was also employed in the reaction to give functionalized spiro[indene-2,3′-pyrrolidines] \(2a-2e\) in satisfactory yields (Fig. 4). The five compounds \(2a-2e\) displayed very similar \(^1\)H NMR spectra, in which only one set of the signs for the characteristic groups in the molecule was observed. This clearly showed only one diastereoisomer existing in the obtained products \(2a-2e\). As for an example, the compound \(2a\) showed three singlets at 3.95, 3.36, 2.51 ppm for the two methoxy groups and one methyl-amino group. The CH\(_2\) unit in the newly-formed pyrrolidine ring reveals two diastereotopic doublets at 2.99, 2.91 ppm with \(J = 16.4\) Hz. The chain CH\(_2\) group connecting to ester scaffold also gives two mixed peaks at 4.39–4.35 and 3.79–3.75 ppm. The single crystal structures of the compounds \(2b\) (Fig. 5) and \(2c\) (SI, Fig. S1) indicated that the aryl group and the methoxycarbonylmethyl group exist at cis-position in the newly-formed pyrrolidine ring.

**Figure 3.** Single crystal structure of compound \(1g\).

**Figure 4.** Synthesis of spiro[indene-2,3′-pyrrolidines] \(2a-2e\).
However, the methoxycarbonyl group stands at opposite direction. This result indicated the configuration of the compound 2a-2e is different to that of the above prepared spiro[indene-2,2′-pyrrolizines] 1a-1i.

When the chain amino acids were employed in the three-component reactions, versatile products with interesting regioselectivity and diastereoselectivity were successfully obtained. At first, the reaction with glycine gave the expected spiro[indene-2,3′-pyrrolidines] 3a-3c in good yields (Fig. 6). The spectroscopy and single crystal structures indicated that an additional moiety of dialkyl maleate was connected to the nitrogen-atom of pyrroline, which obviously came from the addition of free amino group of initially formed pyrroline ring to second molecule of dialkyl acetylenedicarboxylate. The same phenomena is also happened in our previously reported reactions. The single crystal structures of 3a (Fig. 7) and 3c (SI, Fig. S2) showed that the aryl group and the alkoxycarbonylmethyl group exist cis-position in the newly-formed ring of pyrrolidine. Thus, the spiro compounds 3a-3c have the same configuration to that of the above mentioned products 2a-2e. Secondly, the similar reactions with other primary amino acids including alanine, phenylalanine and leucine afforded spiro[indene-2,3′-pyrrolidines] 3d-3n. It should be pointed out that the reactions of phenylalanine and leucine also gave the spiro[indene-2,3′-pyrrolidines] 4h, 4i, 4l and 4n as minor products. This result might be due to the steric hindrance of more substituents in these reactions. Although the spectroscopy of compounds 3d-3n are very similar to that of compounds 3a-3c, the single crystal structures of compounds 3e (Fig. 8), 3h and 3m (SI, Figs S3, S4) clearly revealed that they are belonging to two kinds of structural isomers and diastereoisomers. In the compounds 3a-3c, the aryl group and the alkoxycarbonyl group exist in 2,4-trans-position and the 1,3-dipolar cycloaddition was finished in so-called head-to-tail reaction pattern. In the compounds 3d-3n, the aryl group and the alkoxycarbonyl group exist in 2,3-cis-position. Here, the alkyl groups play an important role for the regioselectivity and diastereoselectivity in the 1,3-dipolar cycloaddition.

At present, the exact addition mechanism and the controlling the effect on stereochemistry is not very clear. For explaining the reaction formation, a plausible 1,3-dipolar cycloaddition reaction process was proposed in Fig. 9. At first, the amino group of amino acid added to the triple bond of the acetylenedicarboxylate to give the adduct (A), which was transferred to a 1,3-dipolar azomethine ylide (B) by elimination of carbon dioxide. The azomethine ylide (B) not only has different conformations (such as C), but also has several resonance forms (B′), which enabled the 1,3-dipolar cycloaddition with variable regioselectivity and diastereoselectivity. Because of the two stronger electron-withdrawing ester groups in the molecule, a isomeric azomethine ylide (B′) could be formed by prototrophic shift of the imine. It was widely accepted that 1,3-dipole with stable anti-conformation reacted with the dipolarophiles according to the endo-approach manner in the concerted 1,3-dipolar cycloaddition reaction. When glycine was used in the reaction (R=H), azomethine ylide (B) added to 2-arylidene-1,3-indanedione through the transition state (D) to give the spiro[indene-2,3′-pyrrolidine] (E). Then, it reacted with another molecular acetylenedicarboxylate to give the spiro compounds 3a-3c. When the substituted amino acids were used in the reaction, the cycloaddition of the azomethine ylide (C′) to 2-arylidene-1,3-indanedione according to another transition state (D′) afforded structurally isomeric spiro[indene-2,3′-pyrrolidines] (E′), which could be separated as the stable products 4h-4n in some cases. At last, reaction of (E′) with excess of acetylenedicarboxylate resulted in the spiro compounds 3d-3n. The azomethine ylides generated from sarcosine and the cyclic amino acids also proceeded with the similar 1,3-dipolar cycloaddition reaction process.

Conclusion

In summary, we have investigated the three-component reaction of α-amino acid, dialkyl acetylenedicarboxylate and 2-arylidene-1,3-indanedione and developed new applications of the new kind of azomethine ylide generated in situ from addition reaction of α-amino acid with dialkyl acetylenedicarboxylate. This reaction provided...
an regioselective and diastereoselective protocol for the synthesis of diverse spiro[indene-2,3′-pyrrolidines],
spiro[indene-2,2′-pyrrolizines] and spiro[indene-2,6′-pyrrolo[1,2-c]thiazoles]. This domino 1,3-dipolar
cycloadition has the advantages of using readily available reagents, mild reaction condition, high diastereoselectivity
and interesting molecular diversity, which would be found high potential applications in the heterocyclic
synthesis.

Figure 6. Synthesis of spiro[indene-2,3′-pyrrolidines] 3a-3n.<ref>

Figure 7. Single crystal structure of compound 3a.<ref>
Methods

Materials. All reactions were performed in atmosphere unless noted. All reagents were commercially available and use as supplied without further purification. NMR spectra were collected on either an Agilent DD2400 MHz spectrometer or a Bruker AV-600 MHz spectrometer with internal standard tetramethylsilane (TMS) and signals as internal references, and the chemical shifts (δ) were expressed in ppm. High-resolution Mass (ESI) spectra were obtained with Bruker Micro-TOF spectrometer. The Fourier transform infrared (FTIR) samples were prepared as thin films on KBr plates, and spectra were recorded on a Bruker Tensor 27 spectrometer and are reported in terms of frequency of absorption (cm⁻¹). X-ray data were collected on a Bruker Smart APEX-2 CCD diffractometer.

General procedure for the three-component reaction of secondary α-amino acids with dialkyl acetylenedicarboxylate and 2-arylidene-1,3-indanediones. A mixture of L-proline or...
thiazolidine-4-carboxylic acid, or sarcosine (1.0 mmol) and dialkyl acetylenedicarboxylate (1.0 mmol) in ethanol (15.0 mL) was stirred at room temperature for twenty minutes. Then, 2-aryliden-1,3-indanidine (0.8 mmol) was added. The mixture was stirred at about 50 °C for ten hours. The solvent was removed at reduced pressure by rotary evaporation, the residue was subjected to preparative thin-layer chromatography (20 × 30 cm² Silica gel GF254) with a mixture of light petroleum and ethyl acetate (V/V = 2:5:1) as eluent to give the pure products 1a-1i and 2a-2e.

General procedure for the three-component reaction of primary α-amino acids with dialkyl acetylenedicarboxylate and 2-arylidene-1,3-indanidines. A mixture of glycine (or alanine, phenylalanine, leucine, 1.0 mmol) and dialkyl acetylenedicarboxylate (4.0 mmol) in ethanol (15.0 mL) was stirred at room temperature for twenty minutes. Then, 2-aryliden-1,3-indanidine (0.8 mmol) was added. The mixture was stirred at about 50 °C for ten hours. The solvent was removed at reduced pressure by rotator evaporation, the residue was subjected to preparative thin-layer chromatography (20 × 30 cm² Silica gel GF254) with a mixture of light petroleum and ethyl acetate (V/V = 2:5:1) as eluent to give the pure product 3a-3n.

Accession codes. Crystallographic data 1g (CCDC 1518094), 2b (CCDC 1518095), 2c (CCDC 1518096), 3a (CCDC 1518097), 3c (CCDC 1518098), 3e (CCDC 1518099), 3h (CCDC 1518100), 3m (CCDC 1518101) have been deposited at the Cambridge Crystallographic Database Centre (http://www.ccdc.cam.ac.uk).

References
1. Nair, V. et al. Strategies for Heterocyclic Construction via Novel Multicomponent Reactions Based on Isocyanides and Nucleophilic Carbones. Acc. Chem. Res. 36, 899–907 (2003).
2. Nair, V., Menon, R. S., Sreekanth, A., Abhilash, N. & Biju, A. T. Engaging Zwitterions in Carbon–Carbon and Carbon–Nitrogen Bond-Forming Reactions: A Promising Synthetic Strategy. Acc. Chem. Res. 39, 520–530 (2006).
3. Nair, V., Deepthi, A., Ashok, D., Raveendran, A. E. & Paul, R. R. 1,4-Dipolar cycloadditions and related reactions. Tetrahedron 70, 3085–3105 (2014).
4. Yavari, I., Piltan, M. & Moradi, L. Synthesis of pyrrol-2(1H)-ones from activated acetylenes, benzoylnitromethanes, and isocyanolines. Tetrahedron 65, 2067–2071 (2009).
5. Ali, M. & Ali, M. Recent progress of isocyanide-based multicomponent reactions in Iran. Beilstein J. Org. Chem. 10, 1577–1586 (2014).
6. Yavari, I., Bayat, M. J., Sirouspour, M. & Souri, S. One-pot synthesis of highly functionalized 1,2-dihydropyridines from primary α-amino acids to acylacetylenes: a facile synthesis of new N-acylvinyl derivatives of amino acids. Tetrahedron 68, 8539–8544 (2012).
7. Sun, J., Yen, C. G. Synthesis of Spiro[indoline-3,3′-piperidin]-2- one Skeleton. Eur. J. Org. Chem. 14, 7928–7930 (2012).
8. Ismail, M., Shaabani, A., Rezayan, A. H. & Sarvary, A. Recent developments in Reissert-type multicomponent reactions. Tetrahedron Lett. 53, 3601–3606 (2012).
9. Sun, J., Yen, C. G. Efficient synthesis of pentasubstituted pyrroles via one-pot thermal-induced [3 + 2] cycloaddition/silica gel-promoted fragmentation sequence between isatin ketonitrones and electron-deficient alkynes. Tetrahedron 69, 4088–4097 (2013).
10. Sun, J., Yen, C. G. Synthesis of Spiro[indoline-3,2′-quinoline]-2,2′-diones via three-component reactions of arylamines, acetylenedicarboxylates, and isatins. Tetrahedron 68, 8539–8544 (2012).
11. Sun, J., Yen, C. G. Synthesis of Spiro[indoline-3,3′-quinoline]-2,2′-diones through a Four-Component Reaction. Eur. J. Org. Chem. 10, 1976–1983 (2012).
12. Sun, J., Sun, Y., Gong, H., Xue, Y. & Yen, C. G. Synthesis of Spiro[indoline-3,2′-pyrrole]-2,2′-diones via three-component reactions of arylamines, acetylenedicarboxylates, and isatins. Tetrahedron 68, 8539–8544 (2012).
13. Sun, J., Sun, Y., Gao, H. & Yen, C. G. Synthesis of Spiro[indoline-3,3′-quinoline]-2,2′-diones through a Four-Component Reaction. Eur. J. Org. Chem. 9, 8–14 (2013).
14. Sun, J., Sun, Y., Gong, H., Xue, Y. & Yen, C. G. Facile Synthesis of Dipyridoxindole-Fused Heterocycles via Domino 1,4-Dipolar Addition and Diels–Alder Reaction of in Situ Generated Huisgen 1,4-Di-Dipole. Org. Lett. 14, 5172–5175 (2012).
15. Sun, J., Sun, Y., Sun, J. & Yen, C. G. Efficient synthesis of pentasubstituted pyrroles via one-pot reactions of arylamines, acetylenedicarboxylates, and 3-phenacylidenoxindoles. Tetrahedron 68, 8256–8260 (2012).
16. Kieland, N. & Lavilla, R. Recent developments in Reissert-type multicomponent reactions. Top. Heterocycl. Chem. 25, 127–168 (2010).
17. Shaabani, A., Rezayan, A. H. & Sarvary, A. Recent progress of isocyanide-based multicomponent reactions in Iran. Mol. Divers. 15, 41–68 (2011).
18. Sun, J., Sun, J., Sun, Y. & Gao, H. Yan, C. G. Development of Domino Reactions with β-Enamino Esters as Key Intermediates. Chin. J. Org. Chem. 32, 1577–1586 (2012).
19. Sun, J., Sun, Y., Wu, Q. & Yan, C. G. Synthesis of Polyfunctionalized Dihydroxyamide. Org. Lett. 16, 3687–3690 (2014).
20. Sun, J., Xia, Y., Wu, Q. & Yan, C. G. Synthesis of Functionalized 2-Aminophenylpyridines and 2-Pyridinones via Domino Reactions of Arylamines, Methyl Propiolate, Aromatic Aldehydes, and Substituted Acetinotrioles. ACS Comb. Sci. 13, 421–426 (2011).
21. Sun, J., Sun, Y., Xue, Y. & Yan, C. G. Synthesis of Functionalized 2-Aminophenylpyridines and 2-Pyridinones via Domino Reactions of Arylamines, Methyl Propiolate, Aldehyde, and Substituted Acetinotrioles. Org. Lett. 13, 436–441 (2011).
22. Sun, J., Wu, Q., Xia, E. Y. & Yan, C. G. General Diversity of Three-Component Reactions of Aromatic Aldehydes, Arylamines, and Acetylenedicarboxylates. Eur. J. Org. Chem. 16, 2981–2986 (2011).
23. Sun, J., Sun, Y., Xue, Y. & Yan, C. G. Selective Synthesis of Fused 1,4- and 1,2-Dihydropyridines by Domino Reactions of Arylamines, Acetylenedicarboxylates, and Cyclic 1,3-Diketones. Eur. J. Org. Chem. 34, 6952–6956 (2011).
24. Ziyaei-Halimehjani, A. & Saidi, M. R. Synthesis of aza-Henry products and enamines in water by Michael addition of amines to thiolaldehydes to activated unsaturated compounds. Tetrahedron Lett. 49, 1244–1248 (2008).
25. Glotova, T. et al. Chemo-, regio- and stereospecific addition of amino acids to acylacetones: a facile synthesis of new N-acetylaminodervatives of amino acids. Tetrahedron 65, 9814–9818 (2009).
26. Li, X., Wang, W. J., Wu, W. & Wu, M. PtCl₂-catalyzed reactions of o-alkynylalanines with ethyl propiolate and dimethyl acetylenedicarboxylate. Tetrahedron 65, 1140–1146 (2009).
27. Yavari, I., Bayat, M. J., Sirouspour, M. & Souri, S. One-pot synthesis of highly functionalized 1,2-dihydropyridines from primary α-amino acids, dialkyl isocyanides, and acetylenic esters. Tetrahedron 66, 7995–7999 (2010).
28. Elasrara, A. Z. & El Khair, A. A. Recent developments in the chemistry of enaminoesters. Tetrahedron 59, 8463–8480 (2003).
29. Nguyen, T. B., Martel, A., Djal, R. & Ducjac, G. N-Benzyl Aspartate Nitrones: Unprecedented Single-Step Synthesis and [3 + 2] Cycloaddition Reactions with Allenes. Org. Lett. 10, 4493–4496 (2008).
28. Zhu, Q. H. et al. L-Proline-catalyzed five-component domino reaction leading to multifunctionalized 1,2,3,4-tetrahydropyridines. *Tetrahedron* **66**, 9721–9728 (2010).

29. Lu, L. et al. A simple and convenient synthesis of 2-(perfluoroalkyl)-4H-chromenes from salicylic N- tosylamines or salicylaldehydes and methyl 2-perfluoralkanoates. *Tetrahedron* **65**, 9152–9156 (2009).

30. Singh, P., Sharma, P. & Bsetty, K. Cycloaddition reactions of cross-conjugated enaminoines. *Tetrahedron* **65**, 8478–8485 (2009).

31. Beznick, J. et al. [2 + 2] Cycloaddition of electron-poor acetylens to (E)-3-dimethylaminol-1-heteroaryl-prop-2-en-1-ones: synthesis of highly functionalized 1-heteroaryl-1,3-butaednes. *Tetrahedron Lett.* **51**, 3392–3397 (2010).

32. Teimouri, M. B. & Abbasi, T. Facile synthesis of oxaspirobutylenes via a domino Michael addition/aldol reaction/γ-lactonization sequence. *Tetrahedron* **66**, 3795–3800 (2010).

33. Das, B., Chinna Reddy, G., Balasubramanyam, P. & Aneyulu, V. An efficient new method for the synthesis of polysubstituted pyroles. *Synthesis* **10**, 1625–1628 (2010).

34. Nagarapu, L., Mallepalli, R., Yeramanchi, L. & Bantu, R. Polyethylene glycol (PEG-400) as an efficient and recyclable reaction medium for one-pot synthesis of polysubstituted pyroles under catalyst-free conditions. *Tetrahedron Lett.* **52**, 3401–3404 (2011).

35. Ramesh, K., Murthy, N. S., Karnakar, K. & Nageswar, Y. DABCO-promoted three-component reaction between amines, dialkyl acetylenedicarboxylates, and glyoxal. *Tetrahedron Lett.* **52**, 3937–3941 (2011).

36. Ghabraie, E., Balalaie, S., Bararjani, M., Biianzadeh, H. R. & Rominger, F. An efficient one-pot synthesis of tetra-substituted pyroles. *Tetrahedron* **67**, 5413–5420 (2011).

37. Sun, J., Chen, L., Gong, H. & Yan, C. G. Convenient synthesis of functionalized spiro[indoline-3,2'-pyrrolizines] or spiro[indoline-3,3'-pyrrolidines] via multicomponent reactions. *Org. Biomol. Chem.* **13**, 5905–5917 (2015).

38. Chen, L., Sun, J., Xie, Y. & Yan, C. G. Molecular diversity of the three-component reaction of α-amino acids, dialkyl acetylenedicarboxylates and N-substituted maleimides. *Org. Biomol. Chem.* **14**, 8479–8507 (2016).

39. Shen, G. L., Sun, J. & Yan, C. G. Diastereoselective synthesis of spiro[benzo[d]pyrrolo-[2,1-b]thiazole-3,3'-indolines] via cycloaddition reaction of N-phenacylbensothiazolium bromides and 3-methylenooxindoles. *Org. Biomol. Chem.* **13**, 10929–10938 (2015).

40. Shi, R. G., Wang, X. H., Liu, R. Z. & Yan, C. G. Two-carbon ring expansion of isatin: a convenient construction of a dibenzo[b,d]azeponine scaffold. *Chem. Commun.* **52**, 6280–6283 (2016).

41. Yang, W. J., Zhang, J., Sun, J., Yan, C. G. Convenient Construction of Indanodione-Fused 2,5-Dihydropyridines, 4,5-Dihydropyridines, and Spirooxindoles, *Eur. J. Org. Chem.* **5416–5423** (2016).

42. Qi, W. J., Han, Y. & Yan, C. G. Diastereoselective synthesis of functionalized cyclopropane-1,3'-indolines and spiro[indoline-3,10-cyclopropane-2,3'-indolines]. *Tetrahedron* **72**, 5057–5063 (2016).

43. Sun, J., Shen, G. L., Huang, Y. & Yan, C. G. Formation of diverse polycyclic spirooxindoles via three-component reaction of isoquinolinium salts, isatins and malononitrile. *Sci. Rep.* **7**, 41024, https://doi.org/10.1038/srep41024 (2017).

44. Jin, G., Suna, J., Yang, R. Y. & Yan, C. G. Stepwise cycloaddition reaction of N-phenacylbensothiazolium bromides and nitroalkenes for tetrahydro-dihydropyrido[2,1-b]thiazoles. *Sci. Rep.* **7**, 46470, https://doi.org/10.1038/srep46470 (2017).

45. Liu, R. Z., Shi, R. G., Sun, J. & Yan, C. G. A. [3 + 2]–[4 + 2]–[3 + 2] cycloaddition sequence of isoquinoline ylide. *Org. Chem. Front.* **4**, 354–357 (2017).

46. Otohiko, T., Shuji, K. & Shigeori, T. Stereochemical study on 1,3-dipolar cycloaddition reactions of heteroaromatic N-ylides with symmetrically substituted cis and trans-olefins. *Bull. Chem. Soc. Jpn.* **58**, 3137–3157 (1985).

47. Allgäuer, D. S., Mayer, P. & Mayr, H. Nucleophilicity Parameters of Pyridinium Ylides and Their Use in Mechanistic Analyses. *J. Am. Chem. Soc.* **135**, 15216–15224 (2013).

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Author Contributions

C.-G.Y. led this research. L.C. and Y.H. performed all the synthetic work and conducted NMR, IR, HRMS. J.S. solved the single crystal X-ray structures and checked all data. Y.Z. Helped to check data and revise paper. C.-G.Y. wrote the paper.

Additional Information

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