Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Organic & Biomolecular Chemistry

RSCPublishing

COMMUNICATION

Cite this: DOI: 10.1039/x0xx00000x

Diene-transmissive hetero-Diels–Alder reaction of 2-vinyl α,β-unsaturated aldimines: stereoselective synthesis of hexahydroquinazolin-2-ones

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Satoru Kobayashi, Kenji Kudo, Ai Ito, Satoru Hirama, Takashi Otani and Takao Saito*

Stereoselective synthesis of hexahydroquinazolin-2(1*H*)-ones has been achieved through the application of diene-transmissive hetero-Diels–Alder methodology to 2-vinyl-1-aza-1,3-butadienes. The cross-conjugated 1-azatriene underwent initial hetero-Diels–Alder reaction on the 1-aza-1,3-butadiene system with tosyl isocyanate to afford the [4+2] mono-cycloadduct pyrimidinone. The second Diels–Alder reaction on the electron-rich 1-amino-1,3-diene unit of the mono-cycloadduct with dienophiles provided hexahydroquinazolin-2(1*H*)-ones with high stereoselectivity.

The diene-transmissive Diels–Alder (DTDA) reaction is an attractive method with which to construct polycyclic ring-fused compounds in an efficient and stereocontrolled manner.[1] The reaction can be simply defined as two sequential Diels–Alder (DA) cycloadditions of cross-conjugate trienes ([3]dendralenes).[2] Thus, the DTDA reaction consists of an initial DA reaction of cross-conjugated triene or its equivalent (masked cross-conjugated triene) with a dienophile, and a subsequent DA reaction with a dienophile on the newly formed diene unit of the mono-cycloadduct. The hetero-Diels–Alder (HDA) reaction is one of the most useful and important tools available for the synthesis of heterocyclic compounds because it can be used for the straightforward construction of heterocycles with predictable chemo-, regio-, and stereoselectivities.[3] Therefore, the diene-transmissive hetero-Diels–Alder (DTHDA) methodology would constitute an efficient and powerful tool for the construction of polycyclic ring-fused heterocycles.[4–10] Nevertheless, examples of this attractive method have so far been limited to reactions with [3]-3-heterodendralenes (thia-,[4] oxa-,[5] and aza-[6,7]), [3]-1-heterodendralenes (oxa-[8,9]), and [3]-1,5-dioxadendralenes,[10] as shown in Fig. 1. Herein, we report the successful implementation of the DTHDA methodology using [3]-1-azadendralenes (cross-conjugated 1-azatrienes) for the first time.

Cross-conjugated azatriene **2** was prepared from the corresponding 2-vinyl α,β-unsaturated aldehyde **1** and amine by condensation with $TiCl_4$ and Et_3N; the product was used without isolation due to its instability in aqueous work-up conditions. *N*-Phenyl azatriene **2a**, prepared *in situ*, reacted with tosyl isocyanate at 80 °C to afford the initial [4+2] cycloadduct, dihydropyrimidinone **3a**, in 97% yield as the sole product (Scheme 1 and Table 1, entry 1). Similarly, azatrienes **2b–d** reacted with tosyl isocyanate to produce [4+2] cycloadducts **3b–d**, respectively, in excellent to good yield (entries 2–4). Notably, the initial DA reaction with tosyl isocyanate took place at the azadiene terminus with complete chemo- and regioselectivity.[11]

Because mono-cycloadduct **3** possesses a pyrimidinone ring system incorporating a newly formed transmitted electron-rich 1-amino-1,3-diene unit, normal electron-demand DA reactions were expected to occur. To examine the π-diastereofacial selectivity of the second DA reaction of **3**, a symmetrical and reactive dienophile, tetracyanoethylene (TCNE), was selected. The reaction of **3a** with TCNE proceeded smoothly at room temperature to afford the [4+2] cycloadduct hexahydroquinazolin-2(1*H*)-one **4a**, in 90% yield as the sole product (Scheme 2 and Table 2, entry 1). Similarly, the reactions of **3b** and **3c** with TCNE produced **4b** and **4c**, respectively, in 97 and 85% yield. The stereochemistry of bis-cycloadduct **4** was determined based on the results of ^{1}H NMR spectroscopic analysis. Nuclear Overhauser effects (NOE) were observed between H-6 and H-8a, and H-5 and H-6 but, as anticipated, not between H-8a and H-4. These observations and the structural information (*trans*-relationship between H-8a and H-4) obtained from X-ray crystallographic analysis of compound **6b** (*vide infra*) suggest that the dienophile (TCNE) attacks the diene π-face from the less hindered back H-4 side of **3**, avoiding the more bulky phenyl substituent at the 4-position.[12]

To examine the *endo*/*exo* selectivity as well as the π-diastereofacial selectivity in the second DA reaction of **3**, the reaction with *N*-

phenylmaleimide (*N*-PhMI) was carried out. The reaction proceeded in toluene at reflux to afford bis-cycloadduct **5** as a single diastereomer in good to excellent yield with complete π-diastereofacial and *endo* selectivities. Thus, *N*-PhMI cycloadded from the less hindered back H-4 side of the diene π-face in the *endo* arrangement.

Finally, the reaction of mono-cycloadduct **3** with methyl vinyl ketone was performed to examine the regioselectivity in addition to the *endo*/*exo* and π-diastereofacial selectivities in the second DA reaction. When diene **3** in toluene was heated to reflux with methyl vinyl ketone (MVK; an excess amount) for 70 h in a sealed tube, the reaction resulted either in the formation of complex mixtures without any cycloadduct (Scheme 4 and Table 4, entry 1), or in the production of **6d** in low yield (17%) with an *endo*/*exo* ratio of 3:1 (entry 2). Fortunately, Lewis acid TMSOTf (20 mol%) was found to effectively catalyze the desired DA reaction to afford **6a** as a single cycloadduct in 53% yield, with no other isomers being detected in the crude reaction mixture (entry 3).[13] TMSOTf also worked effectively in the reactions of **3b–d** to give **6b–d** in moderate to good yields. In all cases, the Lewis acid-catalyzed DA reaction proceeded with complete regio- and stereoselectivity.

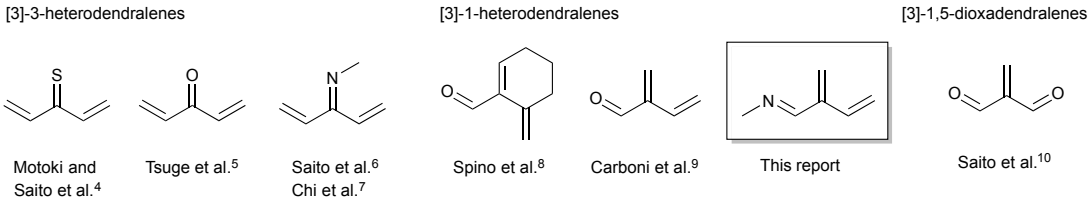
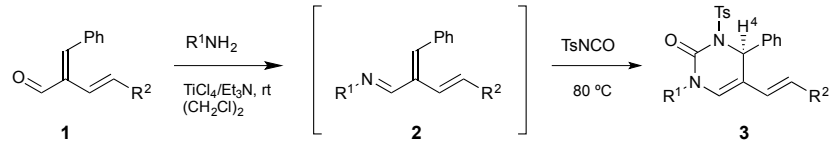


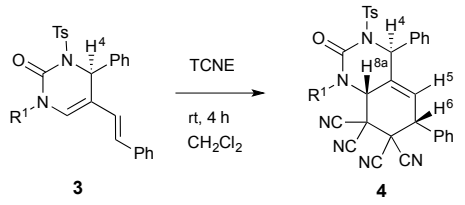
Fig. 1 Reported [3]heterodendralenes used in DTHDA reaction.



Scheme 1 Imination of 2-vinyl α,β-unsaturated aldehyde **1** and initial cycloaddition of azatriene **2** with tosyl isocyanate.

Table 1 Initial cycloaddition of azatriene **2** with tosyl isocyanate

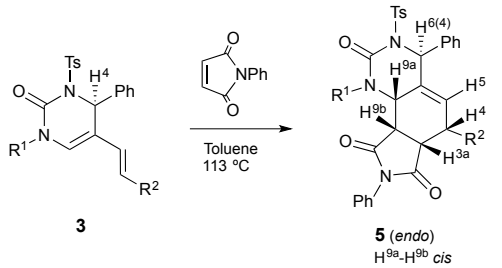
Entry	Azatriene	R^1	R^2	Time (h)	Product	Yield (%)
1	**2a**	Ph	Ph	5	**3a**	97
2	**2b**	*p*-Tol	Ph	4	**3b**	98
3	**2c**	Bn	Ph	3	**3c**	97
4	**2d**	Bn	CO_2Me	2	**3d**	60



Scheme 2 Second cycloaddition of **3** with tetracyanoethylene.

Table 2 Second cycloaddition of **3** with tetracyanoethylene

Entry	Diene	R^1	Product	Yield (%)
1	**3a**	Ph	**4a**	90
2	**3b**	*p*-Tol	**4b**	97
3	**3c**	Bn	**4c**	85



Scheme 3 Second cycloaddition of **3** with *N*-phenylmaleimide.

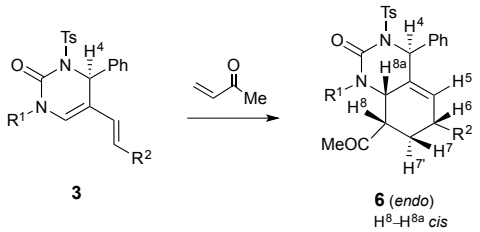
Journal Name RSCPublishing

COMMUNICATION

Table 3 Second cycloaddition of **3** with *N*-phenylmaleimide

Entry	Diene	R^1	R^2	Time (h)	Product	Yield (%)	*endo*/*exo*[a]
1	**3a**	Ph	Ph	10	**5a**	88	>99:1
2	**3b**	*p*-Tol	Ph	18	**5b**	96	>99:1
3	**3c**	Bn	Ph	10	**5c**	98	>99:1
4	**3d**	Bn	CO_2Me	10	**5d**	90	>99:1

[a] Ratio was determined by ^{1}H-NMR spectroscopic analysis. Ratio >99:1 denotes that no *exo*-isomer was detected.



Scheme 4 Second cycloaddition of **3** with methyl vinyl ketone.

Table 4 Second cycloaddition of **3** with methyl vinyl ketone

Entry	Diene	R^1	R^2	Solvent	TMSOTf (mol%)	Temp. (°C)	Time (h)	Product	Yield (%)	*endo*/*exo*[a]
1	**3a**	Ph	Ph	Toluene	—	113[b]	70	**6a**	0	—
2	**3d**	Bn	CO_2Me	Toluene	—	113[b]	50	**6d**	17[c]	3:1
3	**3a**	Ph	Ph	CH_2Cl_2	20	–20 to 0	3.6	**6a**	53	>99:1
4	**3b**	*p*-Tol	Ph	CH_2Cl_2	20	–20 to 0	1	**6b**	63	>99:1
5	**3c**	Bn	Ph	CH_2Cl_2	20	–20 to 0	22	**6c**	56	>99:1
6	**3d**	Bn	CO_2Me	CH_2Cl_2	20	–20 to rt	46	**6d**	43[d]	>99:1

[a] Ratio was determined by ^{1}H NMR spectroscopic analysis. Ratio >99:1 denotes that no *exo*-isomer was detected. [b] Reaction conducted in a sealed tube. [c] 34% recovery of **3d**. [d] 37% recovery of **3d**.

The structure of bis-cycloadduct **6** was determined based on ^{1}H NMR spectroscopic analysis. An *endo* transition-state model of the second DA reaction between **3** and MVK to form bis-cycloadduct **6** is depicted in Fig. 2. An NOE was observed for **6** between H-8 and H-8a, H-7 and H-8a, and between CH_3 protons of the acetyl group and H-7′, which is consistent with the predicted arrangement of MVK (*endo* and orientation). However, NMR spectroscopic techniques were not sufficient to clearly prove the π-facial selectivity of the second DA reaction (relationship between H-4 and H-8a or H-8a and Ph-H at the 4-position). In contrast, X-ray crystallographic analysis of **6b**[14] proved unambiguously the *trans* relationship between H-4 and H-8a (Fig. 3), suggesting that the π-diastereofacial selectivity occurs when MVK cycloadds to the diene from the less hindered H-4 side of **3**. The X-ray crystallographic analysis also confirmed the regio- and *endo* selectivities determined by NOE measurements. We believe that the π-diastereofacial selectivity (from the less hindered H-4 side of **3**) is always the same in the second DA cycloaddition with dienophiles.

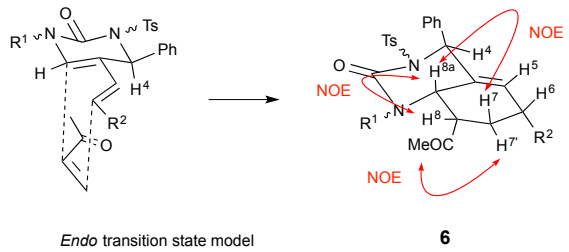


Fig. 2 *Endo* transition-state model and stereochemistry of **6**.

Conclusions

The DTHDA reaction of 2-vinyl *α,β*-unsaturated aldimine has been developed. The reaction, including aza DA reaction with tosyl isocyanate in the initial cycloaddition, provides an efficient new

synthetic route to quinazoline derivatives with high regio-, and stereoselectivities.

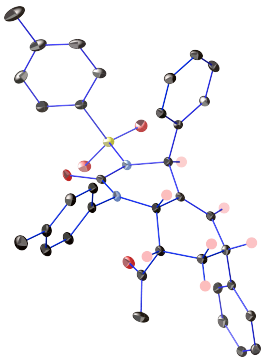


Fig. 3[14] Molecular structure of compound **6b** as an ORTEP plot. Thermal ellipsoids are shown at 30% probability level. Hydrogen atoms on the *p*-tolyl, phenyl, and methyl groups have been omitted for clarity.

Notes and references

1 For reviews on cross-conjugated oligoenes (dendralenes) and for selected precedents on DTDA reactions, see: (*a*) H. Hopf and M. S. Sherburn, *Angew. Chem., Int. Ed*., 2012, **51**, 2298; (*b*) N. A. Miller, A. C. Willis, M. N. Paddon-Row and M. S. Sherburn, *Angew. Chem. Int. Ed.*, 2007, **46**, 937; (*c*) T. A. Bradford, A. D. Payne, A. C. Willis, M. N. Paddon-Row, and M. S. Sherburn, *Org. Lett.*, 2007, **9**, 4861; (*d*) B. Mitasev, B. Yan and K. M. Brummond, *Heterocycles*, 2006, **70**, 367; (*e*) A. D. Payne, A. C. Willis and M. S. Sherburn, *J. Am. Chem. Soc*., 2005, **127**, 12188; (*f*) K. M. Brummond, L. You, *Tetrahedron,* 2005, **61**, 6180; (*g*) O. Kwon, S. B. Park and S. L. Schreiber, *J. Am. Chem. Soc*., 2002, **124**, 13402; (*h*) O. Tsuge, T. Hatta, K. Yakata and H. Maeda, *Chem. Lett*., 1994, 1833; (*i*) W. Adam, T. Deufel, R. Finzel, A. G. Griesbeck and J. Hirt, *J. Org. Chem.*, 1992, **57**, 3991; (*j*) A. Hosomi, T. Masunari, Y. Tominaga, T. Yanagi and M. Hojo, *Tetrahedron Lett.,* 1990, **31**, 6201; (*k*) O. Tsuge, S. Kanemasa, E. Wada and H. Sakoh, *J. Synth. Org. Chem. Jpn*., 1986, **44**, 756 and references cited therein; (*l*) O. Tsuge, E. Wada and S. Kanemasa, *Chem. Lett*., 1983, 239; (*m*) A. T. Blomquist and J. A. Verdol, *J. Am. Chem. Soc*., 1955, **77**, 81; (*n*) W. J. Bailey and J. Economy, *J. Am. Chem. Soc*., 1955, **77**, 1133.

2 The term "Diels–Alder" reaction used here refers to a formal Diels–Alder-type [4+2] cycloaddition, and does not imply a concerted or stepwise reaction mechanism.

3 (*a*) D. L. Boger and S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis;* Academic Press, San Diego, 1987; (*b*) D. L. Boger, *Comprehensive Organic Synthesis;* L. A. Paquette, (vol. Ed); B. M. Trost and I. Fleming, Eds.; Pergamon: Oxford, 1991; Vol. 5, p. 451; (*c*) L. F. Tietze and G. Kettschau, *Top. Curr. Chem*., 1997, **189**, 1; (*d*) S. M. Weinreb, *Top. Curr. Chem*., 1997, **190**, 131; (*e*) P. Buonora, J.-C. Olsen and T. Oh, *Tetrahedron*, 2001, **57**, 6099; (*f*) M. Behforouz and M. Ahmadian, *Tetrahedron,* 2000, **56**, 5259; (*g*) S. Jayakumar, M. P. S. Ishar and M. P. Mahajan, *Tetrahedron*, 2002, **58**, 379; (*h*) K. A. Jørgensen, *Angew. Chem. Int. Ed. Engl.,* 2000, **39**, 3558; and references cited therein. For recent reports on HDA of 1-azadienes, see: (*i*) C. R. Berry and R. P. Hsung, *Tetrahedron*, 2004, **60**, 7629; (*j*) R. C. Clark, S. S. Pfeiffer, M. He, J. R. Strube and J. W. Bode, *J. Am. Chem. Soc.*, 2006, **128**, 8418; (*k*) D. L. Boger, *J. Am. Chem. Soc.*, 2006, **128**, 2587; (*l*) J. Esquivias, R. G. Arrayás and J. C. Carretero, *J. Am. Chem. Soc*., 2007, **129**, 1480.

4 For the DTHDA reaction of [3]-3-thiadendralenes, see: (*a*) S. Motoki, Y. Matsuo and Y. Terauchi, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 284; (*b*) T. Saito, H. Kimura, K. Sakamaki, T. Karakasa and S. Moriyama, *Chem. Commun.*, 1996, 811.

5 For the DTHDA reaction of [3]-3-oxadendralenes, see: (*a*) O. Tsuge, T. Hatta, H. Yoshitomi, K. Kurosaka, T. Fujiwara, H. Maeda and A. Kakehi, *Heterocycles,* 1995, **41**, 225; (*b*) O. Tsuge, T. Hatta, T. Fujiwara, T. Yokohari and A. Tsuge, *Heterocycles,* 1999, **50**, 661.

6 For the DTHDA reaction of [3]-3-azadendralenes, see: (*a*) T. Saito, H. Kimura, T. Chonan, T. Soda and T. Karakasa, *Chem. Commun.,* 1997, 1013; (*b*) T. Saito, S. Kobayashi, M. Ohgaki, M. Wada and C. Nagahiro, *Tetrahedron Lett.,* 2002, **43**, 2627; (*c*) S. Kobayashi, T. Furuya, T. Otani and T. Saito, *Tetrahedron Lett.,* 2008, **49**, 4513; (*d*) S. Kobayashi, T. Furuya, T. Otani and T. Saito, *Tetrahedron,* 2008, **64**, 9715; (*e*) S. Kobayashi, T. Semba, T. Takahashi, S. Yoshida, K. Dai, T. Otani and T. Saito, *Tetrahedron*, 2009, **65**, 920.

7 Very recently, an asymmetric variant of the DTHDA reaction of [3]-3-azadendralene was reported, see: Z. Jin, R. Yang, Y. Du, B. Tiwari, R. Ganguly and Y. R. Chi, *Org. Lett.,* 2012, **14**, 3226.

8 For the DTHDA reaction of [3]-1-oxadendralenes, see: (*a*) C. Spino and G. Liu, *J. Org. Chem.,* 1993, **58**, 817; (*b*) C. Spino, G. Liu, N. Tu and S. Girard, *J. Org. Chem.,* 1994, **59**, 5596; (*c*) C. Spino, B. Hill, P. Dubé and S. Gingras, *Can. J. Chem.,* 2003, **81**, 81; (*d*) A. Dion, P. Dubé and C. Spino, *Org. Lett.,* 2005, **7**, 5601; (*e*) C. Spino, *Synlett,* 2006, 23; (*f*) S. Perreault and C. Spino, *Org. Lett.,* 2006, **8**, 4385.

9 For the DTHDA reaction of [3]-1-oxadendralenes, see: F. Tripoteau, T. Verdelet, A. Hercouet, F. Carreaux and B. Carboni, *Chem. Eur. J.,* 2011, **17**, 13670.

10 A unique example of the DTHDA reaction of [3]-1,5-dioxadendralenes has been reported, see: T. Saito, S. Kobayashi, T. Otani, H. Iwanami and T. Soda, *Heterocycles,* 2008, **76**, 227.

11 We concluded that the reaction proceeds in a stepwise fashion because whereas tosyl isocyanate, with a highly electrophilic cumulenic center, reacted efficiently, tetracyanoethylene, which is much more reactive than tosyl isocyanate based on the frontier molecular orbital calculations (lower LUMO), did not react with azatriene **2** under even harsher reaction conditions.

12 The observed π-diastereofacial selectivity is consistent with our previous study reported (ref. 6). For selected other precedents of selective π-diastereofacial Diels–Alder reactions of vinyl cyclohexenes, see: (*a*) J. Franzén, J. Löfstedt, J. Falk and J.-E. Bäckvall, *J. Am. Chem. Soc.,* 2003, **125**, 14140; (*b*) H. W. Sünnemann, A. Hofmeister, J. Magull, M. G. Banwell and A. de Meijere, *Org. Lett.,* 2007, **9**, 517.

13 The reaction of **3a** catalyzed by other Lewis acids such as $TiCl_4$ (20 mol%) and $BF_3{\cdot}OEt_2$ (20 mol%) did not produce **6a**.

14 CCDC-981131 contains the supplementary crystallographic data for this communication†.

Department of Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku, Tokyo 162-8601, Japan.
E-mail: tsaito@rs.kagu.tus.ac.jp; Fax: +81 (0)3-5261-4631

† Electronic supplementary information (ESI) available: Experimental details and other electronic format see DOI: 10.1039/b000000x//

Journal Name

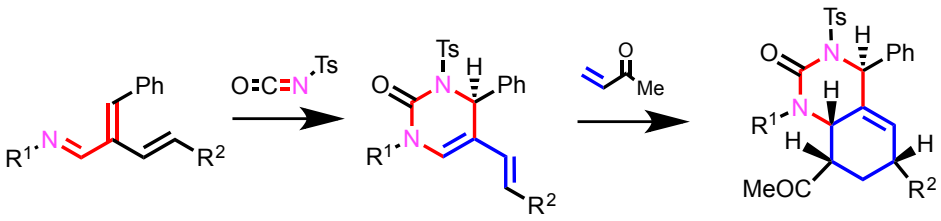
RSCPublishing

COMMUNICATION

Diene-transmissive hetero-Diels–Alder reaction of 2-vinyl α,β-unsaturated aldimines: stereoselective synthesis of hexahydroquinazolin-2-ones

For Table of Contents:

Graphic:



Text:

The tandem Diels–Alder methodology of cross-conjugated 1-azatrienes for synthesis of crossed bis-cycloadducts with high chemo-, regio- and stereoselectivities is described.