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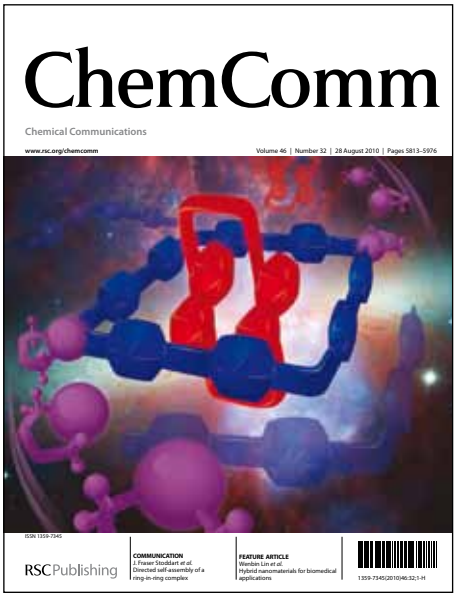

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ARTICLE TYPE

Catalytic asymmetric synthesis of 1,3-enyne scaffolds: design and synthesis of conjugated nitro dienynes as novel Michael acceptors and development of new synthetic methodology

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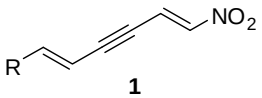
A novel catalytic enantioselective synthesis of functionalized 1,3-enynes have been developed, featuring the design and synthesis of conjugated nitro dienynes as a useful new class of Michael acceptors. Moreover, a simple, yet flexible catalytic cascade approach to functionalized enantioenriched acyclic α,β-enones and cyclic dienones have also been developed.

1,3-Enynes are important structural motifs present in many naturally occurring and drugs[1] such as terbinafine,[2] a potent drug for superficial fungal infections, and calichemicin γ1,[3] an effective antitumor antibiotic. 1,3-Enynes are also versatile building blocks in organic chemistry[4] and material science.[5] Therefore, considerable efforts have been devoted to develop new methods to synthesize 1,3-enynes.[6,7] Whereas several methods have been developed for their racemic synthesis,[6] the asymmetric synthesis, especially catalytic asymmetric synthesis, of 1,3-enynes still remains a challenging task. Recently, Krische group reported elegant Rh-catalyzed enantioselective reductive coupling of 1,3-diynes to α-keto aldehydes and α-hydroxy esters.[7] However, these procedures are only applicable to the synthesis of enantioenriched 1,3-enynes with an allylic stereogenic center. To date, a general, highly enantioselective method for the synthesis of 1,3-enynes with a propargylic stereogenic center has not been achieved.

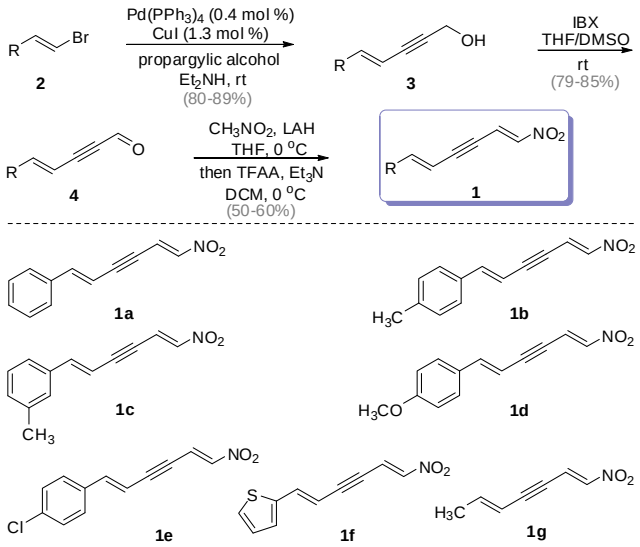
As part of our continuing interest in the catalytic asymmetric syntheses of chiral unsaturated structural motifs and building blocks,[8] herein we report a distinct approach toward the catalytic enantioselective synthesis of 1,3-enynes. This approach featuring for the first time the design and synthesis of conjugated nitro dienynes as a useful new class of Michael acceptors, provides previously inaccessible enantioenriched 1,3-enynes with a propargylic stereogenic center in good yields with high enantioselectivity. Notably, We have further developed a simple, yet flexible novel catalytic cascade approach to functionalized enantioenriched acyclic α,β-enones and cyclic dienones, two classes of synthetically useful compounds.



1
conjugated nitro dienynes

Fig. 1 Design of conjugated nitro dienynes **1** as a new class of Michael acceptors.

To target the synthesis of challenging 1,3-enynes and tackle an issue of broader significance in organic synthesis, conjugated nitro dienynes **1** (Fig. 1) were designed. Whereas nitroolefins as Michael acceptors have been extensively investigated,[9] the closely related conjugated nitro dienynes **1**, have not been designed and synthesized, despite their potential in synthetic chemistry. Thus we began our studies by developing a method for the synthesis of nitro dienynes **1**. As shown in Scheme 1, vinyl bromides **2** underwent Sonogashira coupling with propargylic alcohol, leading to the corresponding alcohols **3** in high yields. Oxidation of the hydroxyl group of **3** with 2-iodoxybenzoic acid (IBX) afforded aldehydes **4**. **4** underwent Henry reaction with $LiAlH_4$ as the base[10] followed by reaction with trifluoroacetic anhydride (TFAA) in the presence of Et_3N produced the desired nitro dienynes **1**. Notably, a variety of aromatic and aliphatic nitro dienynes **1a-g** could be easily prepared with complete stereocontrol.

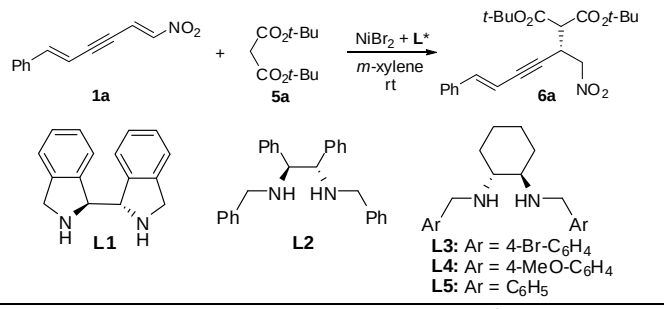


Scheme 1 Synthesis of conjugated nitro dienynes **1**.

With conjugated nitro dienynes **1** in hand, we focused our attention on developing a method for the catalytic enantioselective synthesis of 1,3-enynes, especially with a

propargylic stereogenic center. We envisioned that if nitro dienynes **1** could act as novel extended Michael acceptors,[11] a catalytic enantioselective 1,4-addition (not 1,6- or 1,8-addition)[12] to **1** would provide a route to previously inaccessible 1,3-enynes. To explore the feasibility of this method, the model reaction between nitro dienyne **1a** and di-*tert*-butyl malonate **5a** was investigated. Screening of chiral catalysts indicated that bifunctional thioureas, which have been proved to be effective in the Michael addition of malonates to nitroolefins,[13] did not promote the model reaction. We then turned our attention to chiral metal catalysts. Recently, Huang and co-workers introduced a novel chiral diamine and the corresponding Ni (II) complex. This complex effectively catalyzed the enantioselective Michael addition of di-*tert*-butyl malonate to nitroolefins.[14] Therefore, we applied this complex to conjugated nitro dienyne substrates. Huang's 1:1 $NiBr_2$–**L1** complex[14] promoted the reaction to afford the desired product **6a** in moderate yield (56%) with moderate enantioselectivity (66% ee) (Table 1, entry 1). These results highlighted the difference in reactivity of our nitro dienyne substrates relative to known nitroolefins. Pleasingly, Evans-type chiral Ni (II)-diamine complexes,[15] which have been used extensively in asymmetric catalysis,[16] efficiently catalyzed the model reaction to provide the product **6a** in good yields with high enantioselectivity (entries 2-5). The use of 1:2 $NiBr_2$–**L3** complex afforded 90% yield and 93% ee (entry 3). Finally, screening of solvents showed that *m*-xylene was still optimal.[17]

Table 1 Optimization of the reaction conditions[a]

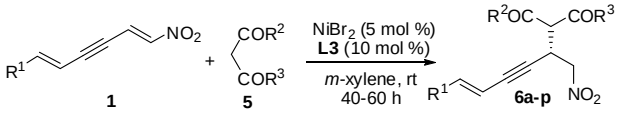


Entry	L	$NiBr_2$-L	Time	Yield[b] (%)	ee[c] (%)
1[d]	**L1**	1:1	24	56	66
2	**L2**	1:2	15	86	–95
3	**L3**	1:2	40	90	93
4	**L4**	1:2	40	87	91
5	**L5**	1:2	40	87	92

[a] All reactions were performed at the 0.2 mmol scale using 1.5 equiv of **5a** with 5 mol % of catalyst. [b] Isolated yields. [c] Determined by chiral HPLC. [d] At 80 °C and 5 mol % PMP was used.

The present reaction serves as a general method for the enantioselective synthesis of functionalized 1,3-enynes. As shown in Table 2, a range of electron-rich and electron-deficient aryl-substituted nitro dienynes **1b-e** proceeded with various 1,3-dicarbonyl compounds smoothly to provide the desired 1,3-enynes in good yields (88-95%) with high enantioselectivity (92-93% ee). Heteroaromatic substituted nitro dienyne **1f** also provided good results (entries 6 and 16). Notably, alkyl-substituted nitro dienynes **1g** was also suitable for this reaction (entries 7 and 10). It is noteworthy that no 1,6- or 1,8-addition was observed in all cases.

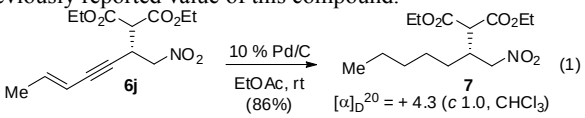
Table 2 Synthesis of various enantioenriched 1,3-enynes[a]



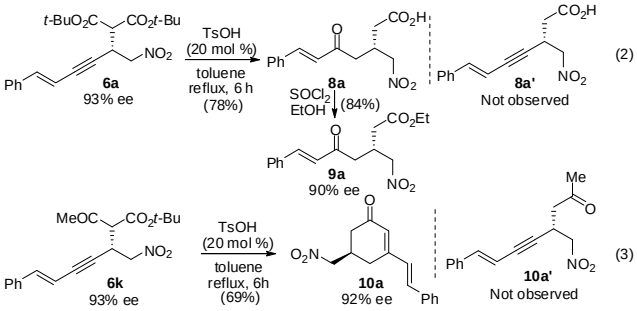
Entry	R^1	R^2	R^3	Yield[b] (%)	ee[c] (%)
1	Ph	O*t*-Bu	O*t*-Bu	**6a**, 90	93
2	4-Me-C_6H_4	O*t*-Bu	O*t*-Bu	**6b**, 93	93
3	3-Me-C_6H_4	O*t*-Bu	O*t*-Bu	**6c**, 90	93
4	4-MeO-C_6H_4	O*t*-Bu	O*t*-Bu	**6d**, 92	93
5	4-Cl-C_6H_4	O*t*-Bu	O*t*-Bu	**6e**, 88	92
6	2-thienyl	O*t*-Bu	O*t*-Bu	**6f**, 90	92
7	Me	O*t*-Bu	O*t*-Bu	**6g**, 85	94
8	Ph	Me	Me	**6h**, 90	90
9	Ph	OEt	OEt	**6i**, 92	93
10	Me	OEt	OEt	**6j**, 87	90
11[d]	Ph	Me	O*t*-Bu	**6k**, 94	93 (93)[e]
12[d]	4-Me-C_6H_4	Me	O*t*-Bu	**6l**, 93	93 (93)[e]
13[d]	3-Me-C_6H_4	Me	O*t*-Bu	**6m**, 92	92 (92)[e]
14[d]	4-MeO-C_6H_4	Me	O*t*-Bu	**6n**, 95	93 (93)[e]
15[d]	4-Cl-C_6H_4	Me	O*t*-Bu	**6o**, 90	92 (92)[e]
16[d]	2-thienyl	Me	O*t*-Bu	**6p**, 90	93 (93)[e]

[a] All reactions were performed at the 0.2 mmol scale using 1.5 equiv of **5**. [b] Isolated yields. [c] Determined by chiral HPLC. [d] 1:1 diastereomeric mixture; determined by ^{1}H-NMR. [e] Enantiomeric excess of the diastereomer.

To determine the absolute configuration, the 1,3-enyne **6j** was converted to the compound **7** (Eq. 1). The (*S*) configuration was established by comparison of the optical rotation of **7** with previously reported value of this compound.[18]



To further demonstrate the utility of enantioenriched 1,3-enynes **6**, these compounds were treated with TsOH for the hydrolysis/decarboxylation reaction. Interestingly, reaction of 1,3-enyne **6a** and **6k** with a catalytic amount of TsOH (20 mol %) did not afford the hydrolysis/decarboxylation products **8a′** and **10a′** but instead directly led to acyclic α,β-enone **8a** (Eq. 2) and cyclic dienone **10a** (Eq. 3) in good yields almost without loss of enantiomeric purity. The enantioselectivity of **8a** was determined via transformation into the corresponding ester **9a**.

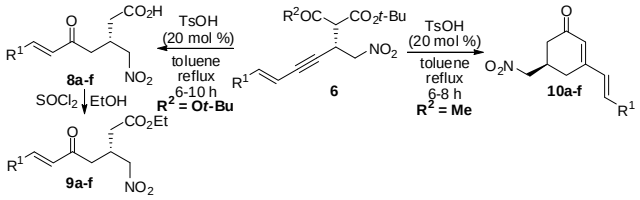


We were excited with these unexpected results as the obtained acyclic α,β-enones and cyclic dienones are synthetically useful but inaccessible compounds. On the other hand, the incorporation of 1,3-enynes leading to the completely regioselective formation of synthetically useful enones is also noteworthy, as there are no reports of TsOH-catalyzed hydration reactions of 1,3-enynes.[19] Only activated aryl alkynes have been previously shown to undergo TsOH-catalyzed hydration to afford the corresponding ketones (non-activated aryl alkynes: 0–9% yields).[20]

In view of the importance of acyclic α,β-enones and cyclic

dienones, we investigated the scope of the cascade reactions. As shown in Table 3, the scope of the reactions was remarkable. Various functionalized acyclic α,β-enones **9a-f** and cyclic dienones **10a-f** were obtained in good yields with high enantioselectivity. While several methods have been developed for the syntheses of acyclic α,β-enones[21] and cyclic dienones,[22] respectively, these reported protocols are not applicable to the synthesis of our acyclic α,β-enones **9** and cyclic dienones **10**. Functionalized acyclic α,β-enones **9** represent a novel class of multifunctional chiral synthons as they contains enone, ester and nitro groups. Due to the vinylogous reactivity, cyclic dienones have been demonstrated as a useful class of substrates in the enantioselective transition-metal catalyzed[23] and organocatalyzed[24] reactions. However, the reported asymmetric reactions used unfunctionalized racemic cyclic dienone substrates.

Table 3 Synthesis of various functionalized enantioenriched acyclic α,β-enones **9** and cyclic dienones **10** [a]



Entry	R^1	**8**, **9**,Yield (%)	**9**, ee [d] (%)	**10**, Yield (%)	**10**, ee [d] (%)
1	Ph	78 [b] (84)[c]	90	69	92
2	4-Me-C_6H_4	85 [b] (85)[c]	91	73	89
3	3-Me-C_6H_4	84 [b] (84)[c]	93	76	90
4	4-MeO-C_6H_4	83 [b] (87)[c]	93	75	88
5	4-Cl-C_6H_4	73 [b] (80)[c]	90	65	90
6	2-thienyl	76 [b] (83)[c]	92	70	90

[a] All reactions were performed with **6** (0.2 mmol) and 20 mol % TsOH under reflux. [b] Isolated yield of **8**. [c] Isolated yield of **9**. [d] Determined by chiral HPLC.

Conclusions

In conclusion, we have developed a novel catalytic enantioselective synthesis of previously inaccessible 1,3-enynes in good yields with high enantioselectivity. This approach features for the first time the design and synthesis of conjugated nitro dienynes as a useful new class of Michael acceptors. Moreover, we have further developed a simple, yet flexible catalytic cascade approach to synthetically useful functionalized enantioenriched acyclic α,β-enones and cyclic dienones.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Representative experimental procedure, compound characterization data, and copies of spectra. See DOI: 10.1039/b000000x/

1 (a) T. Akiyama, K. Takada, T. Oikawa, N. Matsuura, Y. Ise, S. Okada and S. Matsunaga, *Tetrahedron*, 2013, **69**, 6560; (b) N. El-Jaber, A. Estevez-Braun, A. G. Ravelo, O. Munoz-Munoz, A. Rodriguez-Afonso and J. R. Murguia, *J. Nat. Prod*., 2003, **66**, 722; (c) L. Garlaschelli, E. Magistrali, G. Vidari and O. Zuffardi, *Tetrahedron Lett.*, 1995, **36**, 5633.

2 S. L. Iverson and J. P. Uetrecht, *Chem. Res. Toxicol.*, 2001, **14**, 175.

3 N. Zein, A. M. Sinha, W. J. McGahren and G. A. Ellestad, *Science*, 1988, **240**, 1198.

4 (a) W. Zhang, S. Zheng, N. Liu, J. B. Werness, I. A. Guzei and W. Tang, *J. Am. Chem. Soc.*, 2010, **132**, 3664; (b) J. B. Werness and W. Tang, *Org. Lett.*, 2011, **13**, 3664; (c) F. Liu, D. Qian, L. Li, X. Zhao and J. Zhang, *Angew. Chem. Int. Ed.*, 2010, **49**, 6669.

5 K. Campbell, C. J. Kuehl, M. J. Ferguson, P. J. Stang and R. R. Tykwinski, *J. Am. Chem. Soc*., 2002, **124**, 7266.

6 Selected examples: (a) D. Cheng, F. Ling, Z. Li, W. Yao and C. Ma, *Org. Lett*., 2012, **14**, 3146; (b) B. Alcaide, P. Almendros and T. M. del Campo, *Org. Biomol. Chem*., 2012, **10**, 7603; (c) W. Zhang, M. Nishiura and Z. Hou, *Angew. Chem. Int. Ed*., 2008, **47**, 9700; (d) I. M. Lyapkalo and M. A. K. Vogel, *Angew. Chem. Int. Ed*., 2006, **45**, 4019.

7 (a) R. R. Huddleston, H.-Y. Jang and M. J. Krische, *J. Am. Chem. Soc.*, 2003, **125**, 11488; (b) C.-W. Cho and M. J. Krische, *Org. Lett.*, 2006, **8**, 3873.

8 (a) Z. Li, S. Zhang, S. Wu, X. Shen, L. Zou, F. Wang, X. Li, F. Peng, H. Zhang and Z. Shao, *Angew. Chem. Int. Ed.*, 2013, **52**, 4117; (b) B. Fan, X. Li, F. Peng, H. Zhang, A. S. C. Chan and Z. Shao, *Org. Lett*., 2010, **12**, 304; (c) X. Li, X. Li, F. Peng and Z. Shao, *Adv. Synth. Catal*. 2012, **354**, 2873.

9 For a review: O. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem.*, 2002, 1877.

10 S. Belot, A. Massaro, A. Tenti, A. Mordini and A. Alexakis, *Org. Lett*., 2008, **10**, 4557.

11 For a review on extended Michael acceptors: A. G. Csákÿ, G. de la Herrán and M. C. Murcia, *Chem. Soc. Rev*., 2010, **39**, 4080.

12 For a seminal discussion on the regioselectivity of conjugate addition to extended Michael acceptors: N. Krause and S. Tho-rand, *Inorg. Chim. Acta*, 1999, **296**, 1.

13 (a) T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119; (b) J. Ye, D. J. Dixon and P. S. Hynes, *Chem. Commun*., 2005, 4481.

14 Q. Zhu, H. Huang, D. Shi, Z. Shen and C. Xia, *Org. Lett*., 2009, **11**, 4536.

15 D. A. Evans, S. Mito and D. Seidel, *J. Am. Chem. Soc.*, 2005, **127**, 9958.

16 Selected examples: (a) A. Nakamura, S. Lectard, D. Hashizume, Y. Hamashima and M. Sodeoka, *J. Am. Chem. Soc*., 2010, **132**, 4036; (b) C. Fallan and H. W. Lam, *Chem. Eur. J*., 2012, **18**, 11214; (c) J. Chen, J. Chen, Y. Xie and H. Zhang, *Angew. Chem. Int. Ed.*, 2012, **51**, 1024.

17 DCM: 86% yield, 86% ee; Toluene: 75% yield, 78% ee.

18 D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger and J. Zhang, *J. Am. Chem. Soc*., 2002, **124**, 13097.

19 For a review on catalytic hydration of alkynes: L. Hintermann and A. Labonne, *Synthesis*, 2007, 1121.

20 (a) N. Olivi, E. Thomas, J. Peyrat, M. Alami and J. Brion, *Synlett*, 2004, 2175; (b) G. Le Bras, L. Provot, J. Peyrat, M. Alami and J. Brion, *Tetrahedron Lett*., 2006, **47**, 5497.

21 (a) R. G. Kelleher, M. A. McKervey and P. Vibuljan, *J. Chem. Soc., Chem. Commun.*, 1980, 486; (b) K. Tanaka, T. Shoji and M. Hirano, *Eur. J. Org. Chem*., 2007, 2687; (c) M. Lemhadri, Y. Fall, M. Santelli and H. Doucet, *Synthesis*, 2009, 1021.

22 (a) E. Wenkert and M. K. Schorp, *J. Org. Chem*., 1994, **59**, 1943; (b) X. Fu, S. Zhang, J. Yin, T. L. McAllister, S. A. Jiang, C.-H. Tann, T. K. Thiruvengadam and F. Zhang, *Tetrahedron Lett.*, 2002, **43**, 573; (b) M. Tissot, D. Poggiali, H. Henon, D. Mueller, A. Alexakis, L. Guenee and M. Mauduit, *Chem. Eur. J*., 2012, **18**, 8731.

23 (a) H. Hénon, M. Mauduit and A. Alexakis, *Angew. Chem. Int. Ed.*, 2008, **47**, 9122; (b) K.-s. Lee and A. H. Hoveyda, *J. Am. Chem. Soc*., 2010, **132**, 2898.

24 (a) X. Tian, Y.-K. Liu and P. Melchiorre, *Angew. Chem. Int. Ed*., 2012, **51**, 6439; (b) X. Tian and P. Melchiorre, *Angew. Chem. Int. Ed.*, 2013, **52**, 5360.