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Regio- and Stereo-Selective Intermolecular Hydroamidation of Ynamides: An Approach to (*Z*)-Ethene-1,2-Diamides

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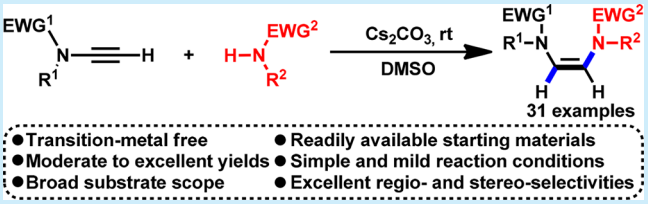
Supporting Information

ABSTRACT: An efficient intermolecular *trans*-selective *β*-hydroamidation of ynamides to furnish a series of (*Z*)-ethene-1,2-diamide derivatives with excellent regio- and stereo-selectivities is described. The *trans*-*β*-addition reactions have been illustrated for a wide range of substrates and proceeded under basic reaction conditions using readily available materials in the absence of a transition-metal catalyst. The synthetic approach to these novel (*Z*)-ethene-1,2-diamide derivatives paves the way for further exploration of their synthetic application.



1,2-Endiamide unit is a unique moiety found in nature cyclic peptides and biologically active compounds.[1] For example, Callyaerin A,[2] Viomycin,[3] and Capreomycin[4] containing 1,2-endiamide unit have been used widely in antituberculosis treatments (see Figure 1). Compared with the extensive

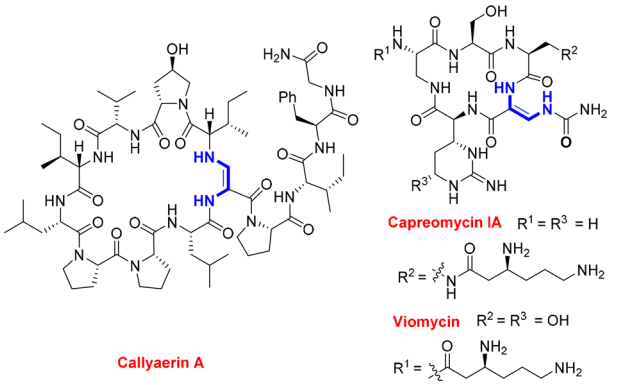


Figure 1. Examples of 1,2-endiamide-containing natural cyclic peptides.

studies of the synthesis of saturated 1,2-diamines,[5] only a few synthetic methods are available for the construction of 1,2-endiamine derivatives, partially because of their poor stability. For example, a method for the synthesis of N^1,N^2,1,2-tetraphenylethene-1,2-diamine under harsh reaction conditions has been reported.[6] In this regard, 1,2-endiamides are useful surrogates, because of their increased stability.[7] However, general synthetic approaches to (*Z*)-ethene-1,2-diamide derivatives, which would have many potential applications in organic and peptide chemistry,[8] are not available yet. Hence, the development of an efficient strategy for the synthesis of (*Z*)-ethene-1,2-diamide derivatives from readily available starting materials is highly desirable.

Hydroamidation reaction of alkyne has emerged as a powerful tool for the construction of enamide derivatives with 100% atom economy and has received considerable attention in the past decades.[9] Ynamides, as special alkynes containing a nitrogen atom bearing an electron-withdrawing group directly attached to the triple bond,[10] have been used as useful and versatile building blocks for the synthesis of a series of unknown nitrogen-containing molecules.[11] For instance, a one-pot alkynylation/intramolecular hydroamidations were reported to yield tetrahydropyrazine derivatives via a *β*-addition of the ynamide intermediates by Urabe's group[12] and Cossy's group,[13] independently. Theoretically, the intermolecular hydroamidation of ynamides would offer an atom-economic approach to 1,2-endiamides. In 2014, Dodd reported an efficient access to *N*-functionalized indoles via an intermolecular *trans*-selective *β*-addition of ynamides with indole derivatives as the nucleophiles.[14] However, the substrate scope of nucleophiles is limited to indoles and other *NH*-containing heteroaromatics and, to the best of our knowledge, the intermolecular hydroamidation of ynamides with simple amides as the nucleophile has been kept unexplored. Recently, our group disclosed that ynamides could be used as racemization-free coupling reagents to facilitate amide and peptide bond formation[15] with *cis*-selective *α*-hydroacyloxylation of carboxylic acids to ynamides under acidic reaction conditions as a key feature. Later, we developed a novel synthetic strategy for ynamides from commercially available starting materials.[16] Herein, we reported an intermolecular *trans*-selective *β*-addition of simple amides to ynamides to afford a broad range of (*Z*)-ethene-1,2-diamides with excellent regio- and stereo-selectivities under basic reaction conditions.

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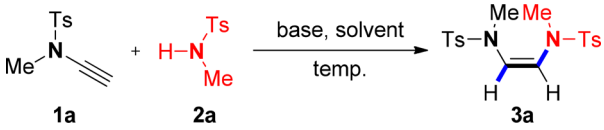
An initial attempt disclosed that the intermolecular hydroamidation reaction of ynamide (**1a**) and *N*,4-dimethylbenzenesulfonamide (**2a**) could indeed afford the target product (*Z*)-ethene-1,2-diamide **3a** with excellent regio- and stereoselectivity (*Z*:*E* > 99:1) in 93% yield with NaH as a base (see Table 1, entry 1). The structure of **3a** was further confirmed by

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3a**

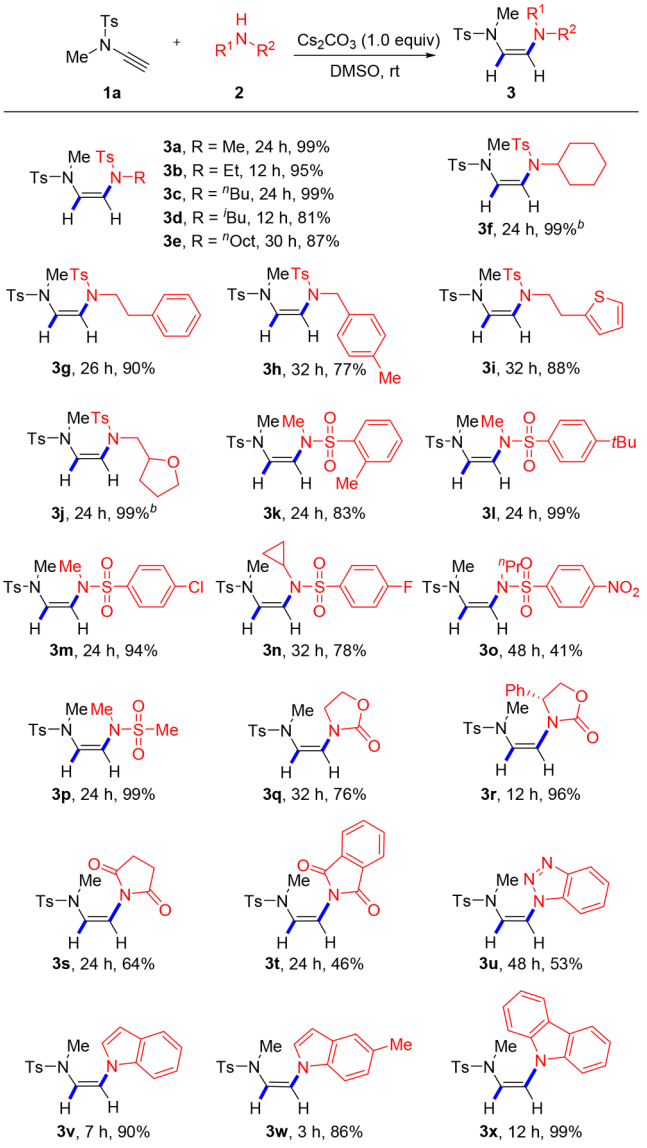
entry	base	solvent	temperature (°C)	time (h)	yield[b] (%)
1	NaH	DMSO	50	14	93
2	^{t}BuONa	DMSO	50	12	61
3	K_2CO_3	DMSO	50	18	20
4	Cs_2CO_3	DMSO	50	8	95
5	NaOH	DMSO	50	20	60
6	Cs_2CO_3	DMSO	rt	24	96
7	Cs_2CO_3	DMF	rt	24	79
8	Cs_2CO_3	THF	rt	48	68
9[c]	**Cs_2CO_3**	**DMSO**	**rt**	**24**	**99**
10[d]	Cs_2CO_3	DMSO	rt	24	89
11[c,e]	Cs_2CO_3	DMSO	rt	24	91

[a]Reaction conditions: unless otherwise specified, the reaction was performed with **1a** (0.2 mmol), **2a** (0.4 mmol), and base (0.4 mmol) in solvent (1.0 mL). [b]Isolated yields. *Z*:*E* > 99:1 (determined by crude ^{1}H NMR). [c]Cs_2CO_3 (0.2 mmol) was used. [d]Cs_2CO_3 (0.1 mmol) was used. [e]**2a** (0.2 mmol) was used.

X-ray crystallography (see the Supporting Information for details). In order to make this reaction as a general approach to (*Z*)-ethene-1,2-diamide derivatives, further optimization of the reaction conditions was performed and the representative results are summarized in Table 1. Base, temperature, and solvent used in this reaction have remarkable effects on the reaction efficiency. Evaluation of the base disclosed that Cs_2CO_3 offered the best result (Table 1, entries 1−5). Decreasing the reaction temperature has a beneficial effect on the reaction efficiency (Table 1, entry 6). Investigations on the solvents revealed that diemthylsulfoxide (DMSO) was the optimal choice (Table 1, entries 7 and 8). Screening of the loading of base identified that 1.0 equiv of Cs_2CO_3 lead to (*Z*)-ethene-1,2-diamide **3a** in quantitative yield (Table 1, entry 9). A clean reaction was observed, even with a stoichiometric amount of **1a** and **2a**, when the reaction was conducted in DMSO at room temperature (Table 1, entry 11).

The substrate scope of the intermolecular hydroamidation reaction was examined after the optimal reaction conditions were established. The ynamide substrate *N*-methyl ynetoluenesulfonamide (MYTsA **1a**) was treated with a series of secondary amides under the optimized reaction conditions, and the results are listed in Scheme 1. For the *N*-alkyl ynetoluenesulfonamides, a broad range of alkyl substituents are tolerated to give the corresponding products (**3a**−**3j**) in good to excellent yields. The evaluation of *N*-alkyl-arylsulfonylamides disclosed that the electronic effects of the aryl rings have little influence on the reaction efficiency (**3k**−**3o**). *N*-Methylmethanesulfon amide, 2-oxazolidones, and succinimide were also compatible in this transformation to afford the desired products (**3p**−**3t**) in 46%−99% yields. In addition, the *NH*-containing aromatic heterocycles, such as benzotriazole,

Scheme 1. Substrate Scope of Secondary Amides[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol) and Cs_2CO_3 (0.2 mmol) in DMSO (1.0 mL) at room temperature (rt). Isolated yields. *Z*:*E* > 99:1 (determined by crude ^{1}H NMR). [b]At 100 °C.

indole, and carbazole, could also exhibit high reactivity with retaintion of excellent regio- and stereo-selectivities to form the hydroamidation products (**3u**−**3x**) in moderate to excellent yields.

Then, the exploration of ynamides revealed that a series of alkyl and aryl substituents on the N atom were all tolerated to furnish the target products (see Scheme 2, **4a**−**4f**) in high to excellent yields. Beside terminal ynamides, internal alkyne sulfonamide was also compatible for this reaction to give desired product **4g** in 66% yield, albeit a higher reaction temperature was required. Interestingly, the hydroamidation products **3b** and **3p** could also be synthesized in 90% and 99% yield by the addition of MYTsA **1a** with the corresponding secondary sulfonamide.[17] Such features offered one more synthetic route for choosing when one of the starting materials is difficult available for certain 1,2-endiamides.

The synthetic utility of this intermolecular hydroamidation reaction was further explored. A gram-scale experiment

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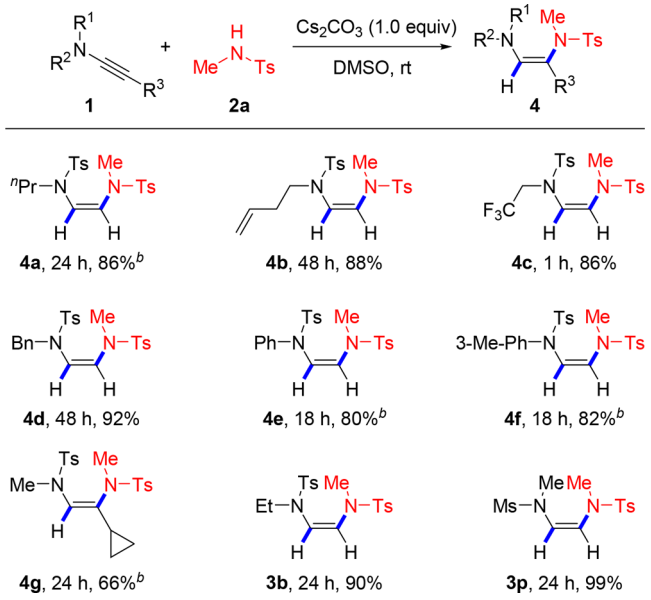
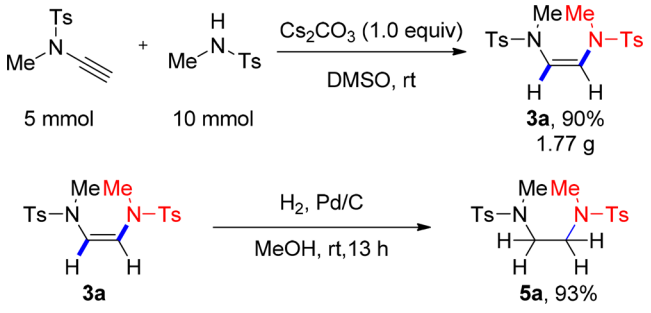
Scheme 2. Substrate Scope of Ynamides[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), and Cs_2CO_3 (0.2 mmol) in DMSO (1.0 mL) at rt. Isolated yields. *Z*:*E* > 99:1 (determined by crude ^{1}H NMR). [b]At 100 °C.

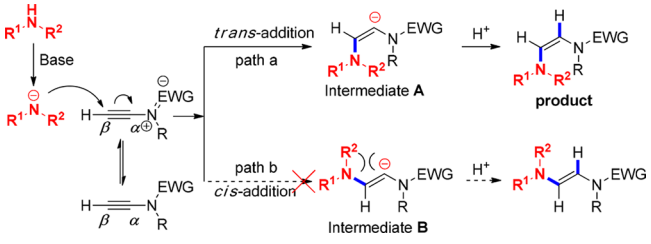
between ynamide **1a** and *N*,4-dimethylbenzenesulfonamide **2a** demonstrated that 1.77 g of the corresponding product **3a** could be obtained in 90% yield. Furthermore, hydrogenation of **3a** in the presence of Pd/C provided ethane-1,2-diamide **5a** in 93% yield (see Scheme 3).

Scheme 3. Gram-Scale Experiment and Synthetic Application



A plausible reaction mechanism was proposed, based on our experimental results (see Scheme 4). Deprotonation of nucleophilic secondary amide by base provides the amide anion $R^1R^2N^-$. The amide functional group of ynamide not only polarized the C−C triple bond but also enabled ynamide to act as an effective 1,4-addition acceptor.[18] Consequently, the *β*-addition of anion $R^1R^2N^-$ to ynamide could generate the anion intermediate **A** or **B** via a *trans*- or *cis*-1,4-addition, respectively. According to the literature, DFT calculations demonstrated that the corresponding free energy of intermediate **A** is lower than that of the intermediate **B**.[14] In other words, coulombic repulsion between the N lone-pair electrons of the R^1R^2N group and the negative charge of carbanion at C_α in intermediate **B** overwhelms the steric hindrance between two amide groups of intermediate **A**. Thus, the formation of *trans*-addition intermediate **A** is favored and the protonation of **A** afforded the final *trans*-addition product with excellent regio- and stereo-selectivity.

Scheme 4. Plausible Reaction Mechanism



In conclusion, we have developed an efficient strategy for the preparation of unknown (*Z*)-ethene-1,2-diamides with excellent regio- and stereo-selectivities, which are difficult to access via the traditional approach. Note that the base-promoted intermolecular *trans*-selective *β*-hydroamidation of ynamides proceeded smoothly in the absence of a transition-metal catalyst. This transformation displays excellent functional group tolerance and broad substrate scopes, with respect to both ynamides and secondary amides. Given the easy availability of starting materials, mild reaction conditions and the potential application of (*Z*)-*β*-endiamides in organic synthesis, a broad interest for this novel approach will be expected.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02409.

Experimental procedures, compounds characterization data, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1840556 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Berer, N.; Rudi, A.; Goldberg, I.; Benayahu, Y.; Kashman, Y. *Org. Lett.* **2004**, *6*, 2543−2545. (b) Pappo, D.; Vartanian, M.; Lang, S.; Kashman, Y. *J. Am. Chem. Soc.* **2005**, *127*, 7682−7683. (c) Vos, S.; Berrisford, D. J.; Avis, J. M. *Biochemistry* **2002**, *41*, 5383−5396.

(2) Ibrahim, S. R.; Min, C. C.; Teuscher, F.; Ebel, R.; Kakoschke, C.; Lin, W.; Wray, V.; Edrada-Ebel, R.; Proksch, P. *Bioorg. Med. Chem.* **2010**, *18*, 4947−4956.

(3) Wallis, M. G.; Streicher, B.; Wank, H.; von Ahsen, U.; Clodi, E.; Wallace, S. T.; Famulok, M.; Schroeder, R. *Chem. Biol.* **1997**, *4*, 357−366.

(4) Wang, M.; Gould, S. J. *J. Org. Chem.* **1993**, *58*, 5176−5180.

(5) (a) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161−3196. (b) Kizirian, J.-C. *Chem. Rev.* **2008**, *108*, 140−205. (c) Zhu, Y.; Cornwall, R. G.; Du, H.; Zhao, B.; Shi, Y. *Acc. Chem. Res.* **2014**, *47*, 3665−3678.

(6) Kornev, A. N.; Sushev, V. V.; Zolotareva, N. V.; Baranov, E. V.; Fukin, G. K.; Abakumov, G. A. *Org. Lett.* **2015**, *17*, 6154−6157.

(7) (a) Balázs, Á.; der Eycken, E. V.; Fülöp, F. *Tetrahedron Lett.* **2008**, *49*, 4333−4335. (b) Zeitler, K.; Steglich, W. *J. Org. Chem.* **2004**, *69*, 6134−6136. (c) Robinson, A. J.; Lim, C. Y.; He, L.; Ma, P.; Li, H.-Y. *J. Org. Chem.* **2001**, *66*, 4141−4147.

(8) (a) Parker, K. A.; Dermatakis, A. *J. Org. Chem.* **1997**, *62*, 4164−4167. (b) Schumann, S.; Zeitler, K.; Jäger, M.; Polborn, K.; Steglich, W. *Tetrahedron* **2000**, *56*, 4187−4195. (c) Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167−3196.

(9) (a) Patel, M.; Saunthwal, R. K.; Verma, A. K. *Acc. Chem. Res.* **2017**, *50*, 240−254. (b) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795−3892. (c) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem. Rev.* **2015**, *115*, 2596−2697.

(10) (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064−5106. (b) Evano, G.; Jouvin, K.; Coste, A. *Synthesis* **2012**, *45*, 17−26. (c) Pan, F.; Shu, C.; Ye, L.-W. *Org. Biomol. Chem.* **2016**, *14*, 9456−9465. (d) Prabagar, B.; Ghosh, N.; Sahoo, A. K. *Synlett* **2017**, *28*, 2539−2555.

(11) (a) Gourdet, B.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 3802−3803. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840−2859. (c) Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, *47*, 560−578. (d) Cook, A. M.; Wolf, C. *Tetrahedron Lett.* **2015**, *56*, 2377−2392. (e) Evano, G.; Blanchard, N.; Compain, G.; Coste, A.; Demmer, C. S.; Gati, W.; Guissart, C.; Heimburger, J.; Henry, N.; Jouvin, K.; Karthikeyan, G.; Laouiti, A.; Lecomte, M.; Martin-Mingot, A.; Métayer, B.; Michelet, B.; Nitelet, A.; Theunissen, C.; Thibaudeau, S.; Wang, J.; Zarca, M.; Zhang, C. *Chem. Lett.* **2016**, *45*, 574−585. (f) Hu, L.; Zhao, J. *Synlett* **2017**, *28*, 1663−1670. (g) Singh, R. R.; Liu, R.-S. *Adv. Synth. Catal.* **2016**, *358*, 1421−1427. (h) Huple, D. B.; Mokar, B. D.; Liu, R. S. *Angew. Chem., Int. Ed.* **2015**, *54*, 14924−14928. (i) Mokar, B. D.; Huple, D. B.; Liu, R. S. *Angew. Chem., Int. Ed.* **2016**, *55*, 11892−11896.

(12) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820−1821.

(13) Aubineau, T.; Cossy, J. *Chem. Commun.* **2013**, *49*, 3303−3305.

(14) Hentz, A.; Retailleau, P.; Gandon, V.; Cariou, K.; Dodd, R. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 8333−8337.

(15) Hu, L.; Xu, S.; Zhao, Z.; Yang, Y.; Peng, Z.; Yang, M.; Wang, C.; Zhao, J. *J. Am. Chem. Soc.* **2016**, *138*, 13135−13138.

(16) Tu, Y.; Zeng, X.; Wang, H.; Zhao, J. *Org. Lett.* **2018**, *20*, 280−283.

(17) Other hydroamidation products, such as **3l** (92% yield), **3m** (96% yield), and **3v** (82% yield), could also be synthesized by the addition of ynamide MYTsA **1a** with the corresponding secondary amides.

(18) Evano, G.; Michelet, B.; Zhang, C. *C. R. Chim.* **2017**, *20*, 648−664.

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Org. Lett. XXXX, XXX, XXX−XXX