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Diastereoselective Syntheses of Functionalized Five-Membered Carbocycles and Heterocycles by a SmI_2-Promoted Intramolecular Coupling of Bromoalkynes and α,β-Unsaturated Esters

Kazunori Takahashi and Toshio Honda*

Faculty of Pharmaceutical Sciences, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan

honda@hoshi.ac.jp

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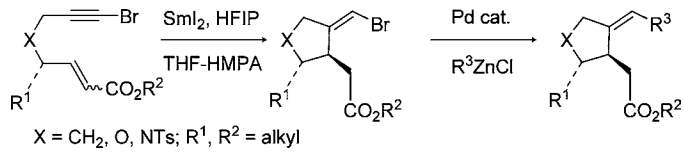
ABSTRACT



An intramolecular coupling of bromoalkynes with α,β-unsaturated esters afforded functionalized five-membered carbocycles and heterocycles with high diastereoselectivities in excellent yields. The vinyl bromides newly generated as the products serve as adequate intermediates for further chemical modification.

There has been increasing interest in the development of new methods for selective syntheses of functionalized small- and medium-sized carbocycles and heterocycles with control of relative and absolute configurations due to both pharmacological applications of many of these cores and the presence of these skeletons in biologically relevant compounds including natural products.[1] An intramolecular coupling reaction of alkynes with activated alkenes provides one of the most promising routes to furnish functionalized cyclic compounds. For this purpose, transition-metal-mediated carbon−carbon bond-forming reactions of alkynes with α,β-unsaturated carbonyl compounds using Rh, Pd, Co, Ni, and Ti complexes remain as outstanding methods for the construction of five-membered cyclic compounds,[2] in which the corresponding metalacycles generated from an intramolecular enyne coupling of the starting materials are involved as intermediates. When this type of reaction was applied to terminus-substituted alkynes, (*E*)-isomers were always isolated as the major products as shown in Scheme 1.

Interestingly, a sequential rhodium-catalyzed silylcarbocyclization of enynes afforded the corresponding (*Z*)-silylated isomer, exclusively, which on a palladium-catalyzed, silicon-based cross-coupling reaction afforded highly substituted cyclopentanes stereoselectively.[2a,b]

An intramolecular samarium diiodide-promoted coupling of aldehydes or ketones with α,β-unsaturated carbonyl compounds via a conjugate addition of ketyl radicals generated in situ is a well-established carbon−carbon bond-forming reaction to give the corresponding cyclization products.[3]

(1) (a) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons: New York, 1983; Vol. 5. (b) Rigby, J. H. *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science Publishers B.V.: Amsterdam, 1988; Vol. 12. (c) Chang, C. W. J.; Scheuer, P. J. *Top. Curr. Chem.* **1993**, *167*, 33–75. (d) Fraga, B. M. *Nat. Prod. Rep.* **1995**, *12*, 303–320. (e) Fraga, B. M. *Nat. Prod. Rep.* **1998**, *15*, 73–92.

(2) Rh catalyst, see: (a) Denmark, S. E.; Liu, J. H.-C. *J. Am. Chem. Soc.* **2007**, *129*, 3737–3744. (b) Denmark, S. E.; Liu, J. H.-C.; Muhuhi, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 14188–14189. Pd catalyst, see: (c) Tsukamoto, H.; Suzuki, T.; Uchiyama, T.; Kondo, Y. *Tetrahedron Lett.* **2008**, *49*, 4174–4177. Co catalyst, see: (d) Chang, H.-T.; Jayanth, T. T.; Wang, C.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 12032–12041. Ni catalyst, see: (e) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911–4920. (f) Ni, Y.; Kassab, R. M.; Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **2009**, *131*, 17714–17718. Ti catalyst, see: (g) Urabe, H.; Suzuki, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 10014–10027.

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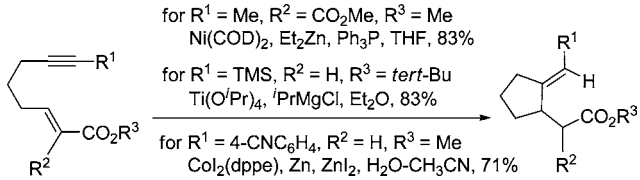
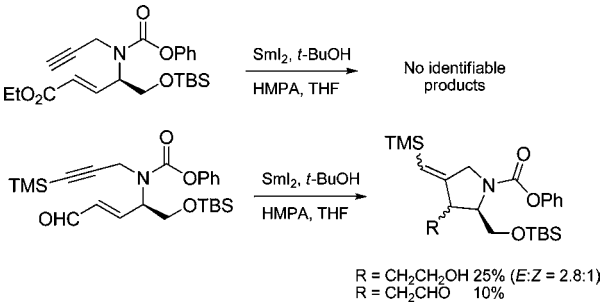
Scheme 1. Previously Reported Transition-Metal-Mediated Enyne Coupling



A similar reaction of alkynes with α,β-unsaturated carbonyl compounds has also been reported as a general synthetic route to cyclic compounds by Moloney,[4] in which the cyclization occurred at the β-position of the enone system, leading to preferential formation of five-membered compounds as the major products. However, low chemical yields as well as poor diastereoselectivities were observed in these carbon−carbon bond-forming reactions, especially in the case of α,β-unsaturated esters due to their low reactivity as shown in Scheme 2.

Scheme 2. Moloney's SmI_2-Mediated Cyclization of Alkynes with Unsaturated Carbonyl Compounds



This report prompted us to investigate a general and efficient samarium diiodide-promoted intramolecular coupling reaction of alkynes with α,β-unsaturated esters, leading to functionalized cyclic products, hopefully with high stereoselectivity, under mild reaction conditions.

We envisaged that the installation of a functional group at the terminal alkyne moiety might enhance the coupling of alkynes with α,β-unsaturated carbonyl compounds since samarium metal would be expected to coordinate with both a functional group on the alkyne and an ester oxygen. The formation of such a relatively rigid structure might facilitate the reactivity of α,β-unsaturated esters.[5] Moreover, if the installed functional group remained untouched during the coupling, it would be a suitable precursor for further chemical modification to highly substituted carbocycles or heterocycles (Figure 1). On the basis of this concept, we decided to introduce a bromine atom to the alkyne moiety, although the corresponding alkynylsamarium was suspected to be formed prior to the expected carbon−carbon bond-forming reaction.[6]

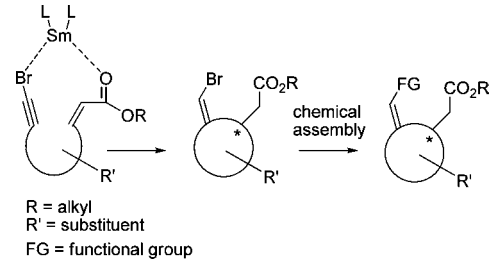


Figure 1. Basic concept for SmI_2-promoted cyclization.

Thus, we investigated a samarium diiodide-promoted intramolecular cyclization of bromoalkynes with α,β-unsaturated esters, and we disclose herein an unprecedented coupling reaction leading to the corresponding five-membered cyclization products with high diastereoselectivities in excellent yields.

We first examined the reaction of 1-ethyl 4,4-dimethyl (1*E*)-7-bromohept-1-en-6-yne-1,4,4-tricarboxylate **1a** with SmI_2 (3 equiv) in THF in the presence of MeOH as a proton source at 0 °C for 1 h; however, none of the cyclized product **2a** was isolated (Table 1, entry 6). When a similar reaction was carried out in the presence of HMPA[7] as an additive, the desired product **2a** was isolated in 64% yield, in which the bromine atom remained on the *exo*-methylene moiety (Table 1, entry 1).

Although the mechanistic rationale for this coupling reaction remains unclear, the presence of a bromine atom seems to play an important role based on the consideration of the previous works,[4] and the desired carbon−carbon bond-forming reaction takes place prior to an alternatively feasible formation of the corresponding alkynylsamarium.

(3) For recent reviews of SmI_2-mediated reaction, see: (a) Soderquist, J. A. *Aldrichimica Acta* **1991**, *24*, 15–23. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68. (c) Molander, G. A. *Org. React.* **1994**, *46*, 211–367. (d) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338. (e) Skrydstrup, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 345–347. (f) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321–3354. (g) Nomura, R.; Endo, T. *Chem.—Eur. J.* **1998**, *4*, 1605–1610. (h) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745–777. (i) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727–2751. (j) Agarwal, S.; Greiner, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2033–2042. (k) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351–10372. (l) Berndt, M.; Gross, S.; Hölemann, A.; Reissig, H.-U. *Synlett* **2004**, 422–438. (m) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371–3403. (n) Jung, D. Y.; Kim, Y. H. *Synlett* **2005**, 3019–3032. (o) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607–637. (p) Rudkin, I. M.; Miller, L. C.; Procter, D. J. *Organomet. Chem.* **2008**, *34*, 19–45. (q) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140–7165. (r) Procter, D. J.; Flowers, R. A., II; Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide*: *A Practical Guide*; Royal Society of Chemistry Publishing: UK, 2010; p 204.

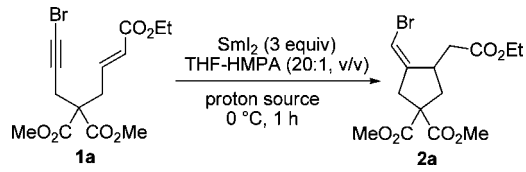
(4) (a) Baldwin, J. E.; Turner, S. C.; Moloney, M. G. *Tetrahedron* **1994**, *50*, 9411–9424. (b) Baldwin, J. E.; Turner, S. C.; Moloney, M. G. *Tetrahedron* **1994**, *50*, 9425–9438.

(5) Medium-sized chelation structure was proposed, see: Helm, M. D.; Silva, M. D.; Sucunza, D.; Findley, T. J. K.; Procter, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9315–9317.

(6) It has been reported that the reaction of iodoalkyne with samarium diiodide afforded the corresponding alkynylsamarium. See: Kunishima, M.; Nakata, D.; Tanaka, S.; Hioki, K.; Tani, S. *Tetrahedron* **2000**, *56*, 9927–9935.

(7) (a) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763–5764. (b) Shabangi, M.; Robert, A.; Flowers, R. A., II *Tetrahedron Lett.* **1997**, *38*, 1137–1140. (c) Prasad, E.; Flowers, R. A., II *J. Am. Chem. Soc.* **2002**, *124*, 6895–6899. (d) Flowers, R. A., II *Synlett* **2008**, 1427–1439. (e) Sadasivam, D. V.; Antharjanam, P. K. S.; Prasad, E.; Flowers, R. A., II *J. Am. Chem. Soc.* **2008**, *130*, 7228–7229.

Table 1. SmI_2-Promoted Coupling in the Presence of a Proton Source



entry	H^+ source (equiv)	yield (%)
1	—	64
2	H_2O (40)	59
3	*tert*-BuOH (5)	67
4	MeOH (1)	74
5	MeOH (5)	76
6	MeOH (5)[a]	0
7	MeOH (10)	77
8	HFIP (1)	77
9	HFIP (5)	79
10	HFIP (10)	78
11	HFIP (40)	77

[a] Starting material (73%) and debrominated compound (18%) were isolated in the absence of HMPA.

Since the expected cyclization was perceived to proceed in moderate yield with the bromine atom remaining, a study was carried out to investigate the best reaction conditions for this conversion, and it was found that the presence of a proton source gave the cyclopentanes in good yields. As can be seen in Table 1, almost all of the proton sources are effective for this coupling. Among them, the use of HFIP (hexafluoroisopropanol)[8] gave the desired product **2a** in 79% yield as the sole product.

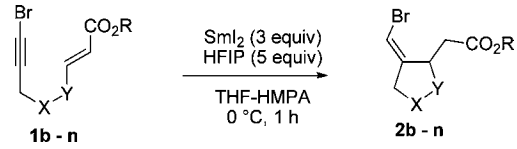
It should be noted that a samarium diiodide-promoted carbon−carbon bond formation of **1a** proceeded via 5-*exo*-dig mode exclusively to provide the cyclopentane **2a**, and no six-membered compound arising from 6-*endo*-dig cyclization was isolated.

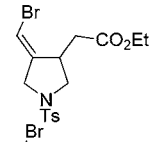
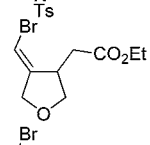
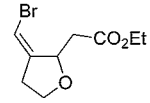
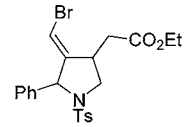
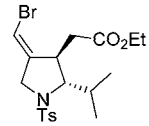
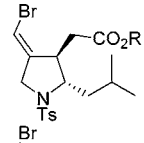
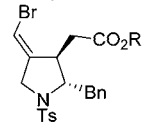
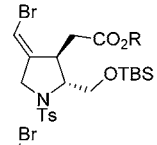
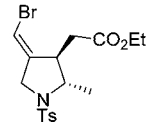
To extend the scope of this carbon−carbon bond formation, syntheses of oxygen and nitrogen heterocycles, often observed in various types of natural products as core fragments,[9] were extensively investigated. The results obtained are summarized in Table 2.

Treatment of **1b** (X = NTs, Y = CH_2) with SmI_2 (3 equiv) in THF−HMPA (20:1, v/v) in the presence of HFIP (5 equiv) at 0 °C for 1 h afforded 3,4-disubstituted pyrrolidine **2b** in 90% yield as the sole product with (*E*)-configuration (entry 1). The stereochemistry of the alkene moiety was determined unambiguously by analysis of its NOE spectrum. The same reaction for ether **1c** (X = O, Y = CH_2) also gave 3,4-disubstituted tetrahydrofuran **2c** in 69% yield with (*E*)-configuration (entry 2). The coupling could be applied to enol ether **1d** (X = CH_2, Y = O), furnishing 2,3-disubstituted tetrahydrofuran **2d** in 66% yield (entry 3). When this reaction was carried out with the starting material **1e** possessing a substituent at the propargylic position, the corresponding pyrrolidine **2e** was obtained as a diastereoisomeric mixture, in a ratio of *trans*:*cis* = 88:12, in 60% yield. In this product, the geometry of the alkene moiety again was confirmed to be (*E*) (entry 4). Further application of the strategy to amine **1f** bearing an (*S*)-isopropyl group at the allylic position gave the 2,3-*trans*-pyrrolidine **2f** diastereoselectively, as a single product, in 81% yield (entry 5).

It can be rationalized on the basis of results shown in Table 2 that the bulkiness of a substituent at the allylic position seems

Table 2. Synthesis of Five-Membered Heterocycles



entry	product		*trans*: *cis*	product; yield [%]
1				**2b**; 90
2				**2c**; 69
3				**2d**; 66
4			88:12[a]	**2e**; 60
5			>99:1	**2f**; 81
6		R = Et	77:23	**2g**; 72
		R =*tert*-Bu	57:43	**2h**; 80
		R = Me	83:17	**2i**; 80
7		R = Et	89:11	**2j**; 73
		R = Me	93:7	**2k**; 79
		R = Et	>99:1	**2j**; 89[b]
8		R = Et	87:13	**2l**; 85
		R = Me	86:14	**2m**; 90
9			70:30	**2n**; 64
			>99:1	**2n**; 91[b]

[a] The relative stereochemistry between 2- and 4-positions is mentioned. [b] (*Z*)-Unsaturated ester is employed as a starting material.

(8) Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, *68*, 3190–3198.

(9) (a) Faulkner, D. J. *J. Nat. Prod. Rep.* **1984**, *1*, 251–280. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 551–598. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1–33. (d) Faulkner, D. J. *Nat. Prod. Rep.* **1987**, *4*, 539–576. (e) Faulkner, D. J. *Nat. Prod. Rep.* **1988**, *5*, 613–663.

to play an important role in control of the stereochemistry at the 3-position of 2,3-substituted pyrrolidines (entries 5−9). By investigation of the ester group, it was found that chemical yields were not influenced by the steric bulk of the ester alkyl group; however, higher diastereoselectivities were observed for methyl and ethyl esters than for the *tert*-butyl group, probably due to the absence of steric hindrance between the substituent at the 2-position and the ester (entry 6). Surprisingly, *trans*:*cis* ratios of the products were greatly improved when the coupling was carried out with the use of the corresponding (*Z*)-unsaturated esters as starting materials (entries 7 and 9).

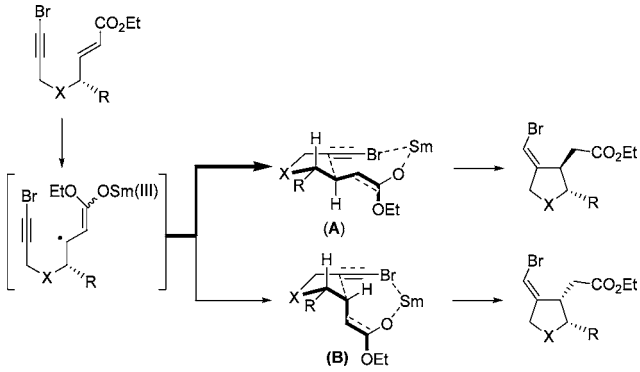


Figure 2. Plausible SmI_2-mediated coupling of (*E*)-α,*β*-unsaturated esters.

Preferential formation of 2,3-*trans*-pyrrolidines from (*E*)-α,*β*-unsaturated esters would be realized based on examination of molecular models of the transition states as depicted in Figure 2, where the transition state (**A**) was preferred to the transition state (**B**) in terms of energetic and steric reasons.

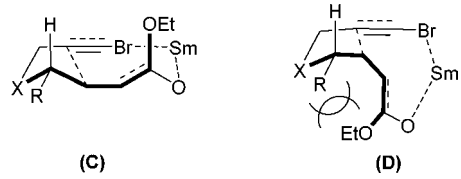
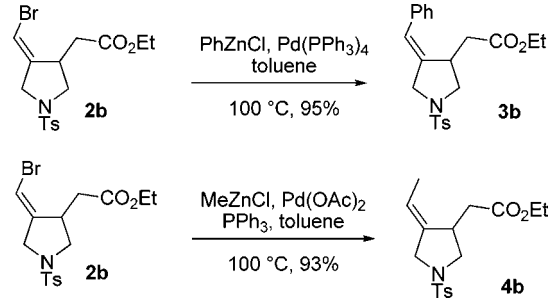


Figure 3. SmI_2-mediated coupling of (*Z*)-α,*β*-unsaturated esters.

The improved *trans*:*cis* ratio for (*Z*)-α,*β*-unsaturated esters is consistent with the mechanistic proposal shown in Figure 3,[10] where severe steric repulsion was observed in the transition state (**D**) leading to the 2,3-*cis*-isomer. Thus, the 2,3-*trans*-isomer from the transition state (**C**) would be a preferential product. In both cases, protonation occurred from the sterically less-hindered side after carbon−carbon bond-forming reaction to furnish the corresponding (*E*)-alkene isomers as major products.[11]

Interestingly, the coupling reaction of *N*-allyl-*N*-(3-bromoprop-2-yn-1-yl)-4-methylbenzenesulfonamide (de-ethoxycarbonyl, **1b**) with samarium diiodide did not take place under the same reaction conditions even in the presence of HMPA. This result might support the hypothesis that the first electron transfer occurred at the α,*β*-unsaturated ester rather than at the triple bond.

Scheme 3. Chemical Modification of the Alkenyl Bromide



An advantage of this reaction is being able to control stereochemistry at the allylic position and to modify the alkenyl bromide newly elaborated in the products leading to highly functionalized five-membered compounds. To prove the potential utility of the bromine atom, a functionalization of alkenyl bromide was attempted by palladium-catalyzed coupling reactions as shown in Scheme 3.

In summary, we were able to establish a general and efficient samarium diiodide-promoted intramolecular coupling reaction of bromoalkynes with α,*β*-unsaturated esters leading to highly functionalized five-membered carbocycles and heterocycles, where the carbon−carbon bond-forming reaction occurred with high diastereoselectivity under mild reaction conditions. We believe that the synthetic strategy developed here has great potential for the synthesis of a wide range of bioactive compounds, including natural products, bearing such a cyclic system.

Acknowledgment. This research was supported financially in part by a grant for The Open Research Center Project and a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Supporting Information Available: Experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) Prasad, E.; Flowers, R. A., II *J. Am. Chem. Soc.* **2002**, *124*, 6357–6361. (b) Honda, T.; Naito, K.; Yamane, S.; Suzuki, Y. *J. Chem. Soc., Chem. Commun.* **1992**, 1218–1219. (c) Hansen, A. M.; Lindsay, K. B.; Antharjanam, P. K. S.; Karaffa, J.; Daasbjerg, K.; Robert, A.; Flowers, R. A., II; Skrydstrup, T. *J. Am. Chem. Soc.* **2006**, *128*, 9616–9617.

(11) When the phenylacetylene derivative was subjected to the same reaction, the (*Z*)-benzylidene derivative (**Z-3b**) was obtained as a major compound (58%, *Z*:*E* = 88:12). On the other hand, a similar reaction of alkyl-substituted alkynes did not give any coupling products. Thus, it is assumed that the substituents on alkynes contributing to stabilization of radicals generated as intermediates is important for this type of cyclization.