ORGANIC LETTERS

2012
Vol. 14, No. 1
326–329

Gold-Catalyzed Three-Component Annulation: Efficient Synthesis of Highly Functionalized Dihydropyrazoles from Alkynes, Hydrazines, and Aldehydes or Ketones

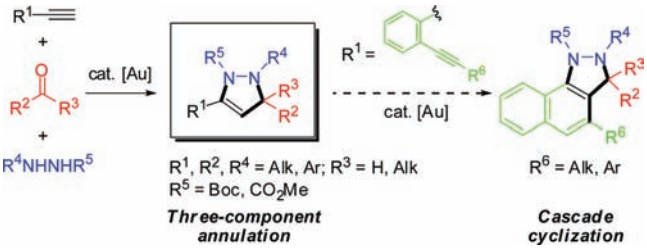
Yamato Suzuki, Saori Naoe, Shinya Oishi, Nobutaka Fujii,* and Hiroaki Ohno*

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

nfujii@pharm.kyoto-u.ac.jp; hohno@pharm.kyoto-u.ac.jp

Received November 15, 2011

ABSTRACT



Polysubstituted dihydropyrazoles were directly obtained by a gold-catalyzed three-component annulation. This reaction consists of a Mannich-type coupling of alkynes with *N,N*′-disubstituted hydrazines and aldehydes/ketones followed by intramolecular hydroamination. Cascade cyclization using 1,2-dialkynylbenzene derivatives as the alkyne component was also performed producing fused tricyclic dihydropyrazoles in good yields.

The development of efficient, direct and environmentally friendly processes has recently garnered much interest in the field of synthetic chemistry. The multicomponent reaction (MCR) is one of the most attractive approaches to achieve this aim, which enables direct construction of the desired molecules having an increased structural complexity from a set of small and simple starting materials.[1] MCRs allow diversity-oriented synthesis of the target compounds by simply changing the substituent(s) of each reaction component. Particularly, ring construction using MCR (multicomponent annulation) is a powerful strategy for facile preparation of diverse polysubstituted cyclic compounds. A transition-metal-catalyzed Mannich-type three-component coupling of alkynes, aldehydes, and amines (A^3 coupling) (eq 1)[2,3] is an attractive reaction not only for facile preparation of propargylamines but also as an elementary reaction for a cascade process. Our group[4] and others[5] have recently

(1) For recent reviews, see: (a) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095–1108. (b) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463–472. (c) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486. (d) Wessjohann, L. A.; Rivera, D. G.; Vercillo, O. E. *Chem. Rev.* **2009**, *109*, 796–814.

(2) For reviews, see: (a) Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472–1483. (b) Li, C.-J. *Acc. Chem. Res.* **2010**, *43*, 581–590.

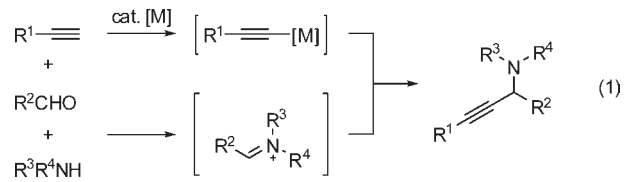
(3) Catalytic Mannich-type coupling reactions of terminal reactions alkynes with isolated nitrones or imines have been also reported. For examples, see: (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245–11246. (b) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319–4321. (c) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497–1499.

(4) (a) Ohno, H.; Ohta, Y.; Oishi, S.; Fujii, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2295–2298. (b) Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 3535–3838. (c) Ohta, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2008**, 835–837. (d) Suzuki, Y.; Ohta, Y.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 4246–4251. (e) Ohta, Y.; Kubota, Y.; Watabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 6299–6302. (f) Ohta, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2009**, *11*, 1979–1982. (g) Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 7052–7058.

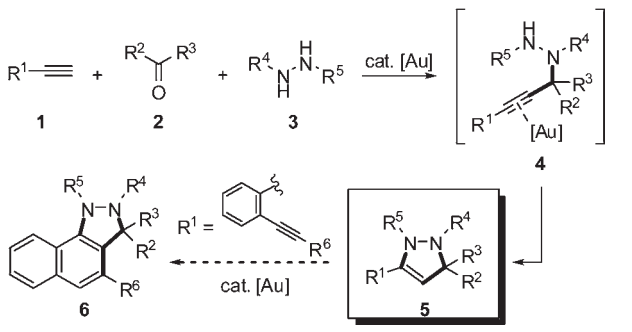
(5) (a) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323–4326. (b) Yoo, W.-J.; Li, C.-J. *Adv. Synth. Catal.* **2008**, *350*, 1503–1506. (c) Zhang, Q.; Cheng, M.; Hu, X.; Li, B.-G.; Ji, J.-X. *J. Am. Chem. Soc.* **2010**, *132*, 7256–7257. (d) Campbell, M. J.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1369–1378. For Rh/Cu-catalyzed double A^3-coupling and [2 + 2 + 2] cycloaddition cascade, see: (e) Bonfield, E. R.; Li, C.-J. *Adv. Synth. Catal.* **2008**, *350*, 370–374.

10.1021/ol203072u
Published on Web 12/16/2011

reported transition-metal-catalyzed cascade reactions including an A^3 coupling and the subsequent nucleophilic cyclization onto an alkyne moiety, leading to heterocyclic compounds. However, to the best of our knowledge, there have been no reports of three-component annulation in which all the reaction components of A^3 coupling are incorporated in the newly formed ring.



Scheme 1. Gold-Catalyzed Three-Component Annulation



Pyrazole derivatives are well recognized as an important class of heterocyclic compounds which exhibit a variety of biological activities.[6] Although a number of approaches to pyrazole derivatives have been developed,[7] they sometimes, especially for polysubstituted ones, suffer from the need for preparation via multistep processes, a limited scope of substituents, and/or regioselectivity in the substitution of two adjacent nitrogen atoms. Hence, development of the multicomponent annulation methodology that provides an efficient and diversity-oriented route to pyrazole derivatives would facilitate the identification of pyrazole-based biologically active molecules.[8] For this purpose, we designed a novel gold-catalyzed three-component annulation of alkynes **1**, aldehydes/ketones **2**, and hydrazines **3** yielding highly functionalized dihydropyrazoles **5** (Scheme 1). This annulation consists of the novel catalytic A^3 coupling using hydrazine derivatives and 5-*endo-dig* intramolecular hydroamination of the resulting propargyl hydrazine **4**. Both reactions are desirably promoted by the same gold catalyst.[9,10] We expected that the regioselectivity can be controlled by differentiation of the electron density of the two nitrogen atoms of the hydrazines. These two nucleophilic groups can serve as the first hydrazonium construction[11] and the consecutive cyclization separately by using two distinctive accessory groups (R^4 and R^5). By utilizing the enamine structure of the resulting dihydropyrazoles **5**, further gold-catalyzed nucleophilic cyclization might produce fused pyrazole derivatives when using alkyne components bearing an additional functionality. Herein we describe a gold-catalyzed annulation[12,13] of alkynes, hydrazines,[14] and aldehydes/ketones for diversity-oriented and regioselective synthesis of pyrazole derivatives. The only waste product of the reaction would be water. Direct synthesis of fused tricyclic compounds **6** via a gold-catalyzed cascade cyclization using 1,2-dialkynylbenzene derivatives as the alkyne component is also described.[15]

Initial investigations focused on the search for suitable catalysts and solvents for the three-component annulation of phenylacetylene (**1a**), isobutyraldehyde (**2a**), and hydrazine derivative **3a** (Table 1). The screening of various

(6) For examples, see: (a) Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819–1824. (b) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347–1365. (c) Yabanoglu, S.; Ucar, G.; Gokhan, N.; Salgin, U.; Yesilada, A.; Bilgin, A. *J. Neural. Transm.* **2007**, *114*, 769–773. (d) Donohue, S. R.; Dannals, R. F.; Halldin, C.; Pike, V. W. *J. Med. Chem.* **2011**, *54*, 2961–2970.

(7) For a recent review, see: Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984–7034.

(8) For multicomponent syntheses of pyrazole derivatives, see: (a) Ahmed, M. S. M.; Kobayashi, K.; Mori, A. *Org. Lett.* **2005**, *7*, 4487–4489. (b) Liu, H.-L.; Jiang, H.-F.; Zhang, M.; Yao, W.-J.; Zhu, Q.-H.; Tang, Z. *Tetrahedron Lett.* **2008**, *49*, 3805–3809. (c) Willy, B.; Müller, T. J. J. *Org. Lett.* **2011**, *13*, 2082–2085.

(9) For gold-catalyzed Mannich-type reactions of terminal alkynes, see: (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584–9585. (b) Lo, V. K.-Y.; Kung, K. K.-Y.; Wong, M.-K.; Che, C.-M. *J. Organomet. Chem.* **2009**, *694*, 583–591. (c) Graf, T. A.; Anderson, T. K.; Bowden, N. B. *Adv. Synth. Catal.* **2011**, *353*, 1033–1038. (d) Cheng, M.; Zhang, Q.; Hu, X.-Y.; Li, B.-G.; Ji, J.-X.; Chan, A. S. C. *Adv. Synth. Catal.* **2011**, *353*, 1274–1278. For a review, see: (e) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917–4938.

(10) The silver-catalyzed cyclization[a] or iodocyclization[b] of propargylhydrazine derivatives have been reported recently, see: (a) Lee, Y. T.; Chung, Y. K. *J. Org. Chem.* **2008**, *73*, 4698–4701. (b) Okitsu, T.; Sato, K.; Wada, A. *Org. Lett.* **2010**, *12*, 3506–3509.

(11) Quite recently, Hashmi *et al.* have reported related iminium-type intermediates (4,5-dihydrooxazoliums) and the nucleophilic attack to these intermediates in gold-catalyzed reactions; see: Hashmi, A. S. K.; Molinari, L.; Rominger, F.; Oeser, T. *Eur. J. Org. Chem.* **2011**, 2256–2264.

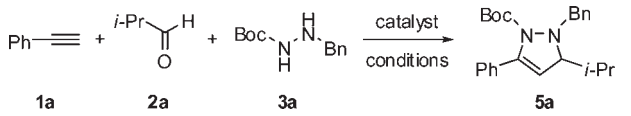
(12) Zhang *et al.* have reported a gold-catalyzed [2 + 2 + 1] annulation of terminal alkynes, nitriles, and an oxygen atom derived from an oxidant yielding 2,5-disubstituted oxazoles; see: He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482–8485.

(13) For reviews on the gold-catalyzed synthesis of heterocycles, see: (a) Hashmi, A. S. K.; Bührle, M. *Aldrichimica Acta* **2010**, *43*, 27–33. (b) Rudolph, M.; Hashmi, A. S. K. *Chem. Commun.* **2011**, *47*, 6536–6544.

(14) For the use of hydrazines in gold-catalyzed conversions, see: (a) Hashmi, A. S. K.; Bührle, M.; Wölfle, M.; Rudolph, M.; Wieteck, M.; Rominger, F.; Frey, W. *Chem.—Eur. J.* **2010**, *16*, 9846–9854. (b) Patil, N. T.; Konala, A. *Eur. J. Org. Chem.* **2010**, 6831–6839. (c) Kinjo, R.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5560–5563. Very recently, He *et al.* have reported gold-catalyzed synthesis of dihydropyrazoles using alkynes and diaziridines; see: Capretto, D. A.; Brouwer, C.; Poor, C. B.; He, C. *Org. Lett.* **2011**, *13*, 5842–5845.

(15) Recently, our group has reported a gold-catalyzed cascade cyclization using diyne derivatives; see: (a) Hirano, K.; Inaba, Y.; Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Adv. Synth. Catal.* **2010**, *352*, 368–372. (b) Hirano, K.; Inaba, Y.; Takahashi, N.; Shimano, M.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 1212–1227. See also: (c) Hirano, K.; Inaba, Y.; Takasu, K.; Oishi, S.; Takemoto, Y.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 9068–9080. Hashimi *et al.* have also reported gold-catalyzed cascade reactions using ene-(di)yne compounds; see: (d) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769–3771. (e) Hashmi, A. S. K.; Grundl, L. *Tetrahedron* **2005**, *61*, 6231–6236. (f) Hashmi, A. S. K.; Häffner, T.; Rudolph, M.; Rominger, F. *Chem.—Eur. J.* **2011**, *17*, 8195–8201.

Table 1. Optimization of Reaction Conditions[a]

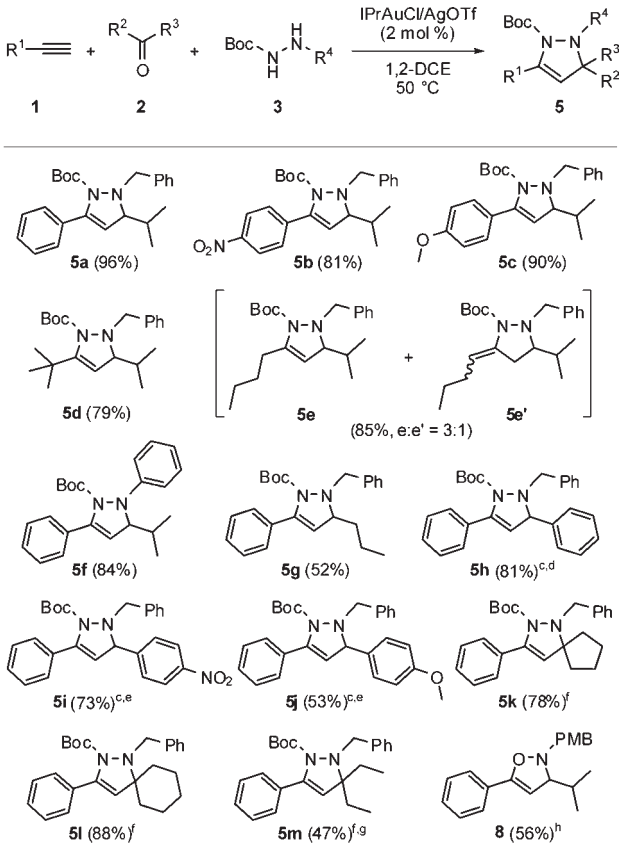


1a 2a 3a 5a

entry	catalyst (mol %)	solvent	T (°C)	time (h)	yield (%)[b,c]
1	CuBr (5)	toluene	50	18	0 (31)
2	$Cu(OTf)_2$ (5)	toluene	50	18	0 (trace)
3	AgOTf (5)	toluene	50	18	6 (45)
4	$AuBr_3$ (5)	toluene	50	20	0 (trace)
5	Ph_3PAuCl (5)	toluene	50	12	0
6	Ph_3PAuCl/AgOTf (5)	toluene	50	2	83
7	Ph_3PAuCl/AgOTf (5)	toluene	rt	3	trace (42)
8	AuCl/AgOTf (5)	toluene	50	12	11 (14)
9	Ph_3PAuCl/AgOTf (5)	MeCN	50	2	72
10	Ph_3PAuCl/AgOTf (5)	EtOH	50	4	73
11	Ph_3PAuCl/AgOTf (5)	AcOH	50	1	88
12	Ph_3PAuCl/AgOTf (2)	AcOH	50	3	87
13	Ph_3PAuCl/AgOTf (2)	1,2-DCE	50	1.5	85
14	IPrAuCl/AgOTf (2)	AcOH	50	3	85
15	**IPrAuCl/AgOTf (2)**	**1,2-DCE**	**50**	**1**	**96**

[a] The reaction was carried out with **3a** (0.18 mmol), **1a** (1.2 equiv), and **2a** (1.2 equiv). [b] Isolated yields. [c] Yields in parentheses show those of propargylamine **4a**.

alkynophilic transition metal catalysts was performed at 50 °C in toluene. The reaction with CuBr, a widely used catalyst for A^3-coupling,[2,4,5d] afforded the propargyl hydrazine **4a** in 31% yield without producing the annulation product **5a** (entry 1). Contrary to our expectation, $AuBr_3$, reported as an efficient catalyst for A^3-coupling,[5c,9] showed almost no activity toward A^3-coupling using hydrazine **3a** as the amine component, yielding only a trace amount of **4a** (entry 4). On the other hand, use of 5 mol % of Ph_3PAuCl/AgOTf resulted in efficient conversion to give a good yield of dihydropyrazole **5a** (83%, entry 6), while the use of AgOTf or Ph_3PAuCl alone proved unsuccessful (entries 3 and 5). The phosphine ligand is important for both the A^3 coupling and cyclization (entry 8). It is noteworthy that the reaction performed at room temperature led to formation of the propargyl hydrazine **4a** (entry 7), which strongly supports the reaction mechanism shown in Scheme 1.[16] The solvent screening (entries 9−13) revealed that acetic acid or 1,2-dichloroethane (1,2-DCE) improved the reaction rate and provided high yields even with a decreased loading of the catalyst (entries 11−13). Finally, the most efficient conversion was observed when using an *N*-heterocyclic carbene (NHC) ligand IPr [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] in 1,2-DCE (entry 15) instead of triphenylphosphine.



[a] Unless otherwise stated, the reaction was carried out using **3** (0.18 mmol), **1** (1.2 equiv) and **2** (1.2 equiv). [b] Isolated yields are shown in parentheses. [c] A modified protocol using **2** (2 equiv) in AcOH was employed. [d] The reaction was carried out at rt. [e] 2.0 equiv of **1** was used. [f] 5 mol % of catalysts were used. [g] 5.0 equiv of **2** was used. [h] The reaction was carried out using a nitrone (0.18 mmol) prepared from **2a** and PMBNHOH **7**, **1** (1.2 equiv) and DIPEA (0.1 equiv) at 70 °C.

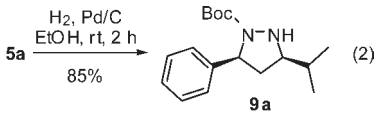
Figure 1. Evaluation of Reaction Scope.[a,b]

Having established the effective reaction conditions for the three-component annulation, we evaluated the reaction scope using other alkynes, hydrazines, and aldehydes/ketones (Figure 1). For terminal alkynes, a range of substituents (R^1) were tolerated including benzene rings bearing an electron-withdrawing or -donating group

(16) Other pathways producing the propargyl hydrazine **4**, for example, initial formation of a propargyl alcohol from an alkyne **1** and a carbonyl compound **2** followed by substitution at the propargylic position, are also conceivable. However, the following observation would support our proposed mechanism shown in Scheme 1: the two-component reaction of phenylacetylene **1a** and isobutyraldehyde **2a** under the optimized conditions (Table 1, entry 15) afforded multiproducts containing a small amount of the propargyl alcohol. Unfortunately, for synthesis of **5m** (Figure 1), premixing of a hydrazine and a ketone in 1,2-DCE at 50 °C for 1 h before addition of the catalysts and phenylacetylene had no effect on the yield, presumably due to the reversible nature of the iminium formation.

(**5b** and **5c**; 81% and 90%, respectively) and a bulky alkyl group (**5d**; 79%), although 1-hexyne afforded an inseparable mixture of the dihydropyrazole **5e** and its regioisomer **5e′** (3:1; 85% combined yield).[17] The use of hydrazine bearing a phenyl group as R^4 instead of a benzyl group was also successful (**5f**; 84%). Similarly, other aliphatic or aromatic aldehydes gave the desired annulation products (**5g**−**j**) under the slightly modified reaction conditions in some cases: for aromatic aldehydes, acetic acid was the solvent of choice to obtain better yields of **5**. It is worth noting that ketones can be used in this reaction if an increased amount of the catalyst (5 mol %) was utilized.[18] Using cyclopentanone or cyclohexanone, spirocyclic dihydropyrazoles **5k** and **5l** were obtained in good yields (78% and 88%, respectively). Furthermore, an acyclic ketone was also suitable for the reaction to give **5m** albeit in modest yield (47%). In addition, we expected these reaction conditions to be applicable for the synthesis of 2,3,5-trisubstituted dihydroisoxazoles by using hydroxylamine derivatives instead of hydrazines. In this reaction, the nitrones generated from aldehydes and hydroxylamines might play the same role as the hydrazonium cation.[3a] However, the reaction using phenylacetylene (**1a**), isobutyraldehyde (**2a**), and PMBNHOH (PMB = 4-methoxybenzyl) (**7**) gave the desired dihydroisoxazole **8** in only low yield. In contrast, by using the isolated nitrone (prepared from **2a** and **7**) and diisopropylethylamine (DIPEA) as an additive, **8** was obtained in moderate yield (56%) (see Supporting Information for details).

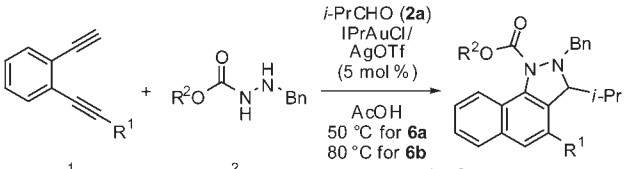
This reaction provides a convenient access to tetrahydropyrazoles. For example, removal of the benzyl group from the dihydropyrazole **5a** under the standard conditions accompanied hydrogenation of a dihydropyrazole ring to afford 3,5-*cis*-tetrahydropyrazole **9a** stereoselectively (eq 2).



(2)

Finally, we turned our attention to the domino process through the three-component annulation, utilizing the enamine structure of the resulting dihydropyrazoles. To our delight, by using 1-ethynyl-2-(phenylethynyl)benzene **10a** as an alkyne component, the three-component annulation and subsequent cyclization proceeded smoothly to provide the benzene-fused dihydroindazole **6a** in good yield (84%, Scheme 2). Use of the diyne **10b** bearing an alkyl group for R^1 and the methyl carbamate **3b** also led to the desired tricyclic product **6b** in 65% yield.

Scheme 2. Gold-Catalyzed Cascade Cyclization[a]



[a] The reaction was carried out using **10**, **2a** (2.0 equiv), and **3** (1.2 equiv).

In summary, we have developed a novel gold-catalyzed three-component annulation of alkynes, hydrazines, and aldehydes/ketones for the direct synthesis of polysubstituted dihydropyrazoles. This reaction shows broad substrate scope for each reaction component and furnished various types of substituted products from a set of simple and easily available starting materials. Use of 1,2-diethynylbenzene derivatives as the alkyne component produces fused tricyclic compounds via the gold-catalyzed cascade cyclization. Application of these dihydropyrazole and fused heterocyclic scaffolds for the development of biologically active molecules is underway.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Integrated Organic Synthesis" (H.O.) and the Targeted Proteins Research Program from the Ministry of Education, Culture, Sports, Science and Technology of Japan. Y.S. is grateful for Research Fellowships from the JSPS for Young Scientists.

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

(17) Removal of the Boc group of the mixture of **5e** and **5e′** afforded the corresponding 4,5-dihydro-1*H*-pyrazole derivative as a single product (see Supporting Information for details).

(18) A gold-catalyzed A^3-coupling using cyclic ketones has been reported recently.[9d]