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Solvent-Dependent Chemoselectivity in Ruthenium-Catalyzed Cyclization of Iodoalkyne–Epoxide Functionalities

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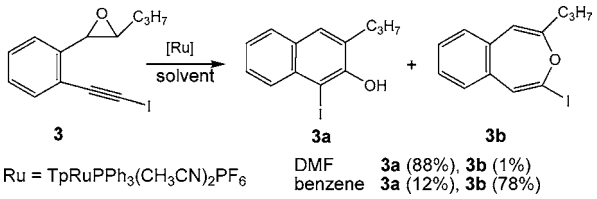
ABSTRACT

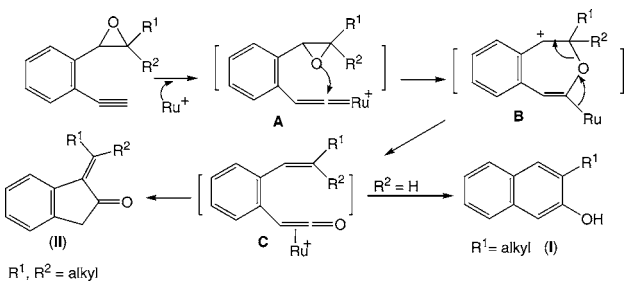


Treatment of 1-(2′-iodoethynylphenyl)-2-propyloxirane (3) with $TpRuPPh_3(CH_3CN)_2PF_6$ catalyst (10 mol %) produced 1-iodo-2-naphthol (3a) exclusively in DMF, but gave 2-iodobenzo[*d*]oxepin (3b) efficiently in benzene. Such a solvent-dependent chemoselectivity suggests a solution equilibrium between ruthenium–π-iodoalkyne and ruthenium–2-iodovinylidene intermediates.

Catalytic cyclization is an important synthetic method to construct useful carbocyclic and heterocyclic frameworks.[1,2] Although the epoxide is a common and practical functionality like an alkyne and alkene, only a few catalytic reactions have been developed for the coupling of epoxides with other functional groups.[3,4] As one example,[4] ruthenium-catalyzed cyclization transformed epoxide−alkyne functionalities into alkene−ketene intermediates, and ultimately gave 2-naphthols **I** or 1-alkylidene-2-indanones **II** depending on the nature of the ruthenium−vinylidene species **A**,[5] of which the epoxide attacks the vinylidene Cα carbon to produce cyclic ruthenium ether intermediate **B**.

Electrophilic metal species can activate an alkyne functionality toward nucleophilic attack, and this approach facilitates many useful catalytic reactions.[6] We seek to realize catalytic cyclizations of epoxide/alkyne functionalities via intramolecular attack of an epoxide at the metal−π-alkyne functionality as depicted in Scheme 2; this cyclization may proceed via a 6-*exo-dig* or 7-*endo-dig* pathway. Here we report a new ruthenium-catalyzed cyclization of 1-(2′-

Scheme 1



(1) Selected reviews: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (c) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. (d) Schore, N. E. In *Comprehensive Organometallic Chemistry*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Hegedus, L. S., Eds.; Pergamon Press: Oxford, UK, 1995; Vol. 12, p 703. (e) Geis, O.; Schmalz, H. *Angew. Chem. Int. Eng.* **1998**, *37*, 911. (f) Fruhauf, H. W. *Chem. Rev.* **1997**, *97*, 523.

(2) For selected examples, see: (a) Brummond, K. M.; Lu, J. *J. Am. Chem. Soc.* **1999**, *121*, 5087. (b) Tobisu, M.; Chatani, N.; Asaumi, T.; Amako, K.; Ie, Y.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12663. (c) Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 5818. (d) Chatani, N.; Morimoto, T,; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 5335. (e) Chatani, N.; Tobisu, M.; Asaumi, T.; Murai, S. *Synthesis* **2000**, 925. (f) Shibata, T.; Toshida, N.; Takagi, K. *Org. Lett.* **2002**, *4*, 1619. (g) Seo, J.; Chui, H. M. P.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 476. (h) Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* **2002**, *124*, 10008. (i) Yamamoto, Y.; Takagishi, H.; Itoh, K. *J. Am. Chem. Soc.* **2002**, *124*, 6844.

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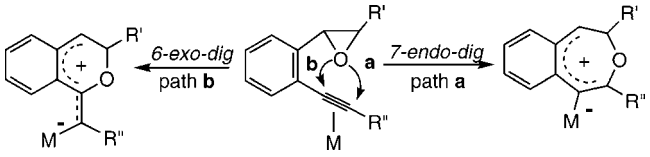
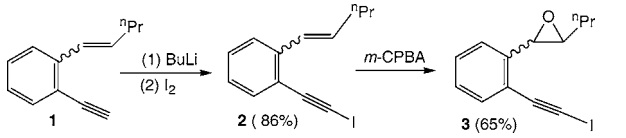
Scheme 2



iodoethynylphenyl)-2-alkyloxiranes with unusual solvent-dependent chemoselectivities.[7] In this cyclization, the active species is a ruthenium−π-iodoalkyne in benzene, but a ruthenium−2-iodovinylidene in DMF. Notably, the epoxide attacks the π-iodoalkyne functionality in a highly regioselective 7-*endo-dig* cyclization.

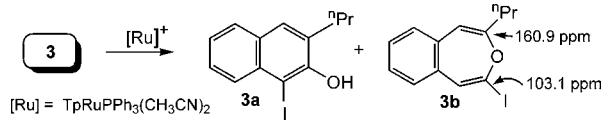
Scheme 3 shows the synthetic procedure for the preparation of the desired 1-(2′-ethynylphenyl)-2-propyl oxirane **3**

Scheme 3



from readily available (*o*-ethynylphenyl)pent-1-ene **1**.[4] Treatment of compound **1** with BuLi (1.0 equiv) in cold THF (−78 °C), followed by I_2 addition, gave iodoalkyne species **2** in 86% yield.[8] Subsequent epoxidation of this product with *m*-CPBA in CH_2Cl_2 (0 °C, 8 h) delivered epoxide **3** in 65% yield. As shown in Table 1, we examined the cyclization of

Table 1. Chemoselectivity in the Cyclization of Epoxide **3** in Various Solvents



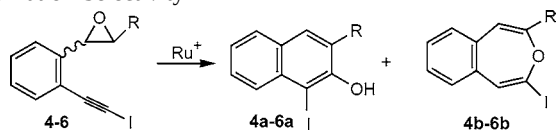
entry	Solvent[a]	temp (time)	products (yields)[b]
1	benzene	80 °C (10 h)	**3a** (12%), **3b** (78%)
2	toluene	95 °C (12 h)	**3a** (16%), **3b** (68%)
3	DCE	80 °C (6 h)	**3a** (28%), **3b** (56%)
4	DME	80 °C (5 h)	**3a** (31%), **3b** (50%)
5	DMF	90 °C (2 h)	**3a** (88%), **3b** (1%)
6	CH_3CN	80 °C (6 h)	NR[c]

[a] 10 mol % of catalyst, [substrate]= 0.56 M. [b] Isolated yields from a silica column. [c] NR= no reaction.

epoxide **3** in benzene (80 °C, 10 h) using $TpRuPPh_3(CH_3CN)_2PF_6$ catalyst[4] (Tp = tris(1-pyrazolyl) borate, 10 mol %). Separation of the crude products on a silica column gave 1-iodo-2-naphthol **3a** and 2-iodobenzo[*d*]oxepin **3b** in 12% and 78% yields, respectively. For **3a**, the ^1H NMR signal of the hydroxyl group appeared at δ 5.83 ppm; this signal enables us to determine its structure on the basis of the proton NOE effect.[9] The intensity of this NMR resonance became small in the presence of CD_3OD. The structure of the seven-membered ring ether **3b** is determined by the proton NOE effect[9] and ^{13}C NMR data; the four tertiary carbon signals of **3b** were found at 160.9, 134.5, 135.1, and 103.1 ppm, respectively. The C6 carbon resonance (103.1 ppm) matches well with that (δ 107.8 ppm) of 6-iodo-3,4-dihydro-2*H*-pyran.[10] Such a cyclization is surprising because it represents a 7-*endo-dig* pathway rather than the expected 6-*exo-dig* mode.[11] Toluene, dichloroethane (DCE), and dimethoxyethane (DME) also gave a mixture of **3a** and **3b** without improving selectivity for either **3a** or **3b** (entries 2−4). Acetonitrile failed to show catalytic activity. In contrast, *N*,*N*-dimethylformamide (DMF) shows excellent selectivity toward 1-iodo-2-naphthol (**3a**) with a yield up to 88%.

The solvent-dependent chemoselectivity is synthetically useful because it gives two cyclized products selectively with the same substrate. We expanded the scope of this cyclization by alternating the epoxide substituents. As shown in Table 2, a small ethyl group as in compound **4** gave small yields

Table 2. The Change of Epoxide Substituents on the Cyclization Selectivity



entry	epoxide	solvent[a]	temp (time)	yields[b]
1	**4**: R = Et	DMF	95 °C (2 h)	**4a** (40%), **4b** (14%)
2	**4**	benzene	80 °C (12 h)	**4a** (7%), **4b** (39%)
3	**5**: R = *i*-Pr	DMF	95 °C (2 h)	**5a** (79%)
4	**5**	benzene	80 °C (12 h)	**5a** (38%), **5b** (45%)
5	**6** : R = n-C_5H_{11}	DMF	95 °C (2 h)	**6a** (87%)
6	**6**	benzene	80 °C (12 h)	**6a** (18%), **6b** (62%)

[a] 10 mol % of catalyst, [substrate]= 0.56 M. [b] Isolated yields from a silica column.

of the desired cyclized products in benzene (7% **4a** and 39% **4b**) and DMF (40% **4a** and 14% **4b**) although similar solvent effects were observed (entries 1−2). Epoxides **5** and **6** bearing isopropyl and pentyl groups also maintain good

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(5) See recent reviews: (a) Bruneau, C. *Top. Organomet. Chem.* **2004**, *11*, 125. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.

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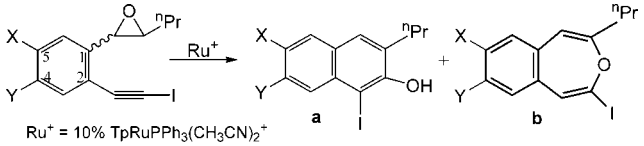
selectivity in DMF (entries 3 and 5), and gave 79% and 87% respective yields of 1-iodo-2-naphthols **5a** and **6a**. In hot benzene, epoxide **6** was more selective in the production of benzo[*d*]oxepin **6b** (62% yield, entry 6), compared to its isopropyl analogue **5**, which gave a 45% yield of ether **5b** in addition to **5a** (38%, entry 4). The nature of the epoxide substituent is very crucial for the selectivity of the ether products.

Table 3 shows the effects of phenyl substituents of substrates on their reaction chemoselectivity. We prepared

Table 3. Ruthenium-Catalyzed Cyclization of Epoxide with Iodoalkyne Functionality



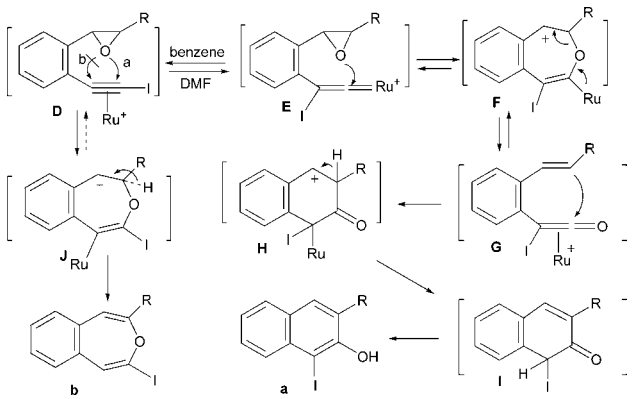
entry	epoxide	solvent[a]	yields[d]
1	**7**: X = F, Y = H	DMF[b]	**7a** (83%)
2	**8**: X = Cl, Y = H	DMF	**8a** (87%)
3	**9**: X = H, Y = F	DMF	**9a** (81%), **9b** (3% [e])
4	**10**: X = H, Y = Me	DMF	**10a** (77%), **10b** (4%[e])
5	**11**: X = OMe, Y = H	DMF	**11a** (85%)
6	**7**	benzene[c]	**7a** (8%), **7b** (81%)
7	**8**	benzene	**8a** (16%), **8b** (71%)
8	**9**	benzene	**9a** (11%), **9b** (76%)
9	**10**	benzene	**10a** (12%), **10b** (63%)
10	**11**	benzene	**11a** (67%), **11b** (4%[e])

[a] 10 mol % of catalyst, [substrate] = 0.56 M. [b] 95 °C (2 h). [c] 80 °C (12 h). [d] Yields were isolated from a silica column. [e] Yields were estimated from NMR spectra.

epoxides **7**−**11** bearing different substituents such as fluoride, chloride, methyl, and methoxy groups at their C4 or C5 carbons. These epoxides showed excellent selectivity for 1-iodo-2-naphthols **7a**−**11a** in DMF (entries 1−5) and gave **7a**−**11a** in 77−87% yields. The structures of **7a** and **9a** were confirmed by the ^{1}H-NOE effect. Epoxides **7**−**10** maintained their preferences for formation of 2-iodobenzo[*d*]oxepins **7b**−**10b** in hot benzene (entries 6−10); the yields were 63−81%. In contrast, epoxide **11** bearing a 5-methoxyphenyl group was still active in the production (67% yields) of 1-iodo-2-naphthol **11a** even in hot benzene.

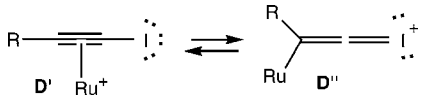
Scheme 4 shows a plausible reaction mechanism to rationalize the solvent-dependent chemoselectivity. We propose that a polar solvent like DMF[12] enhances the

Scheme 4



oxidative addition of ruthenium center into the C−I bond of the substrate, and gives iodoruthenium alkynyl species **E**, which subsequently undergoes a 1,3-iodo shift to give 2-iodovinylidene species **F**. The transformation of species **F** to 1-iodonaphthan-2-ol **a** is similar to that proposed in the mechanism of the catalytic conversion[4] of (*o*-ethynylphenyl) epoxide to phenol (see Scheme 1). Nonpolar solvent benzene is expected to give π-iodoalkyne species **D** predominantly because the oxidative addition of ruthenium becomes very slow. Attack of the epoxide oxygen at the π-iodoalkyne functionality of species **D** follows a 7-*endo-dig* cyclization (path a) to generate a 7-oxa-benzocyclo heptene intermediate **I**, and ultimately gives the expected 6-iodo-7-oxa-benzocycloheptene **b**. The ether product **b** does not undergo 7-oxahept-1,3,5-triene/phenol rearrangement[13] because a substituent was present at both the C(1) and C(6) carbons.

This proposed mechanism is supported by precedents in the literature.[7,8] A catalytic transformation involving 2-iodovinylidene species **F** was reported in a tungsten-catalyzed cyclization of (*o*-iodoethynylbenzene)alkene derivatives.[8] The lack of such an equilibrium in the cyclization of (*o*-ethynylphenyl) epoxide[4] (Scheme 1) reflects the higher electrophilicity of ruthenium−π-iodo alkyne **D** than its



unsubstituted ruthenium−π-alkyne analogue. The structure **D″** not only enhances the electrophilicity of an iodoalkyne functionality but also controls the regioselectivity of the cyclization, which favors the formation of 7-oxa-benzocycloheptenyl ether (path a, 7-*endo-dig*) rather than a six-membered ether derivative (path b, 6-*exo-dig*). The concept of structure **D″** arises from the recent report on the acid-catalyzed carbocyclization of siloxyalkynes with arenes and alkenes.[14]

(7) Although many metal-catalyzed transformations of terminal alkynes[5] proceed via metal−vinylidene intermediates, only two cases show solvent-dependent selectivity arising from an equilibrium between tungsten−vinylidene and tungsten−π-alkyne species, see: (a) Iwasawa, N.; Maeyama, K.; Kusama, H. *Org. Lett.* **2001**, *3*, 3871. (b) Kusama, H.; Yamabe, H.; Iwasawa, N. *Org. Lett.* **2002**, *4*, 2569.

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(9) The ^{1}H NOE maps of cyclized products **3a** and **3b** are provided in the Supporting Information.

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(14) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204.

Table 2 shows significant effects of the alkyl substituent of epoxides on the yields and selectivity of cyclized products **4a**−**6a** and **4b**−**6b**. Our previous study[4] indicates that only a large alkyl substituent facilitates ring-cleavage of oxacarbenium species **G** and gives ruthenium−π-ketene species **H**. In this manner, a large alkyl substituent favors the selectivity of 1-iodo-2-naphthols. This rationale is consistent with our observation that the isopropyl and *n*-pentyl species **5** and **6** gave increasing yields of 2-naphthols **5a** and **6a** in hot benzene when compared to its *n*-propyl analogue **3**. An equilibrium likely exists between species **F** and **G**.

In summary, we found that the cyclization of 1-(2′-iodoethynylphenyl)-2-alkyloxiranes gave 1-iodo-2-naphthol derivatives in DMF very efficiently, but preferably yielded 2-iodobenzo[*d*]oxepin in benzene. The active intermediates in DMF and benzene were ruthenium−2-iodovinylidene and π-iodoalkyne species, respectively. The intramolecular attack of epoxide at the π-iodoalkyne intermediate preferably proceeds via a *7-endo-dig* cyclization, and this unusual pathway is attributed to the electronic effect of an iodo substituent.

Acknowledgment. The authors wish to thank the National Science Council, Taiwan for supporting this work.

Supporting Information Available: NMR spectra and spectral data of new compounds **3**, **3a**−**3b**, **4**−**11**, **4a**−**11a**, and **4b**−**10b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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