

Catalytic monoalkylation of 1,2-diols

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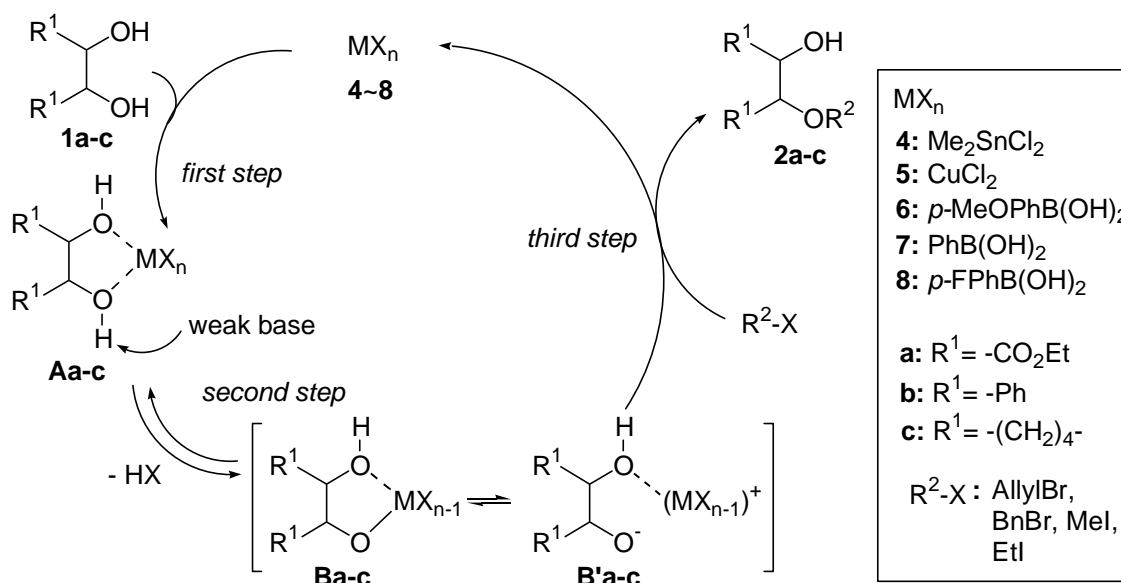
Abstract- A catalytic monoalkylation of 1,2-diols by using a weak base has been developed. Copper(II) dichloride and boronic acids are effective catalysts for activating 1,2-diols in the presence of potassium carbonate as a base. Various 1,2-diols were selectively monoalkylated with allyl-, benzyl- and alkyl- halides in DMF by choosing a suitable catalyst for each 1,2-diol.

Selective monoalkylation of 1,2-diols is an important transformation for organic synthesis. Various methods have been developed to achieve direct monoalkylation of one of two hydroxyl groups in 1,2-diols. Usually an excess amount of 1,2-diols is used.¹ Therefore, many stoichiometric methods have been developed, such as reductive cleavage of acetals,² use of polymer resins,³ thallium salts,⁴ monosodium salts,⁵ silver oxide,⁶ dibutyltin oxide,⁷ arylboronic acid⁸ and direct allylation of 1,2-diols through intramolecular dehydrohalogenation.⁹ However, only a few catalytic processes have been demonstrated for limited examples utilizing tin dichloride,¹⁰ phase transfer catalysts,¹¹ and crown ether.¹² Thus, development of a general, highly selective, and convenient catalytic protocol for monoalkylation of 1,2-diols remains to be exploited.

We have developed the methods for catalytic monoalkylation of 1,2-diols in which 1,2-diols are selectively activated with Lewis acid such as dimethyltin dichloride¹³ or copper(II) salts¹⁴ in the presence of a weak base. We envisioned that this process could be extended to catalytic monoalkylation of 1,2-diols. We present here a general catalytic monoalkylation method for 1,2-diols catalyzed by copper(II) salt or boronic acids under mild condition.

Key words: Diol; Alkylation; Lewis acid; Allylation, Benzylation

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Scheme 1. Working hypothesis for 1,2-diols selective monoalkylation catalyzed by Lewis acid.

Our working hypothesis for selective monoalkylation of 1,2-diols is depicted in Scheme 1. Here MX_n **4-8** and $R^2\text{-X}$ represent Lewis acids and alkylating reagents, respectively. The monoalkylation process is roughly divided into three steps: 1) 1,2-diol **1a-c** is recognized by M^{n+} because of its bidentate character of forming complex **Aa-c**; 2) complex **Aa-c** is selectively deprotonated by weak base, such as metal carbonate affording alkoxide **Ba-c** because of its lowered pKa value than **1a-c** through association with **4-8**; 3) since **Ba-c** (or **B'a-c**) has a higher reactivity than **1a-c**, it is selectively monoalkylated by $R^2\text{-X}$. The resulting monoalkylated product **2a-c** can not coordinate with **4-8**, therefore second alkylation of **2a-c** does not proceed.

Based on this concept, we employed allyl bromide as $R^2\text{-X}$ and diethyl L-tartrate (**1a**) as a diol for initial test of various Lewis acids as catalysts (Eq. 1). The results are summarized in Table 1.

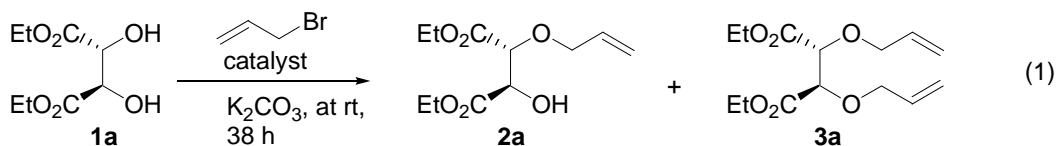


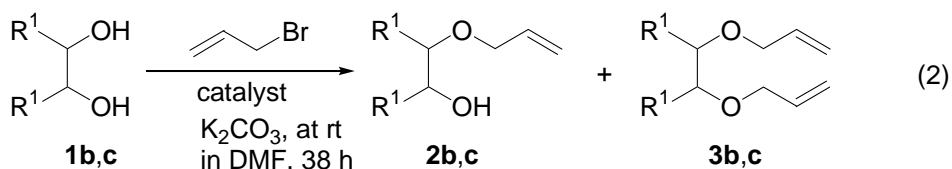
Table 1. Catalytic monoallylation of **1a**.^a

run	catalyst	solvent	Yield (%) ^b	
			2a	3a
1	Me ₂ SnCl ₂ (4)	THF	12	nd ^c
2	4	CH ₂ Cl ₂	21	trace
3	4	DMF	50	2
4	CuCl ₂ (5)	DMF	86	trace
5	<i>p</i> -MeOPhB(OH) ₂ (6)	DMF	23	trace
6	PhB(OH) ₂ (7)	DMF	21	2
7	<i>p</i> -FPhB(OH) ₂ (8)	DMF	27	3

^a To a mixture of **1a**, K₂CO₃ (1.5 equiv), and catalyst (0.1 equiv) in solvent was added allyl bromide (2 equiv). The mixture was stirred for 38 h at rt. ^b Isolated yield. ^c Not detected.

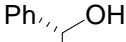
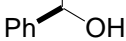
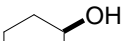
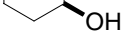
First, we examined dimethyltin dichloride (**4**) as a catalyst, which has been used to effectively catalyze monobenzylation of diols,^{13a} for monoallylation of **1a** with allyl bromide. Use of THF or CH₂Cl₂ led to monoallylated product **2a** obtained in only 12% or 21% yield (runs 1 and 2), while the yield of **2a** was improved in DMF (run 3). Change of catalyst to CuCl₂ (**5**) instead of **4**, led to an improved yield for **2a** (86% yield) (run 4). Phenylboronic acids **6-8** were not effective for this reaction (runs 5-7). In all cases, the formation of diallylated product **3a** was negligible.

Encouraged by this impressive results, we examined the system for *dl*-hydrobenzoin (**1b**) and *cis*-cyclohexane-1,2-diol (**1c**) (Eq. 2). The results are summarized in Table 2.



In this case, however, **5** did not effectively catalyze monoallylation of **1b** and **1c**, affording a disappointing yield of 15% and 4% for **2b** and **2c**, respectively (runs 2 and 7). Replacement of **5** with catalyst **4** slightly improved the yields of **2b** and **2c** (runs 1 and 6), while boronic acids **6-8** efficiently catalyzed monoallylation of **1b** and **1c** (runs 3-5, 8-10). More interestingly, substituents at *para*-position on phenylboronic acids showed opposite effect on the catalytic ability with respect to **1b** and **1c**. That is, for monoallylation of **1b**, **6** substituted with electron donating methoxyl group improved the yield of **2b**, while **8** substituted with electron deficient fluoro group gave lower yield (runs 3-5). On the contrary, for that of **1c**, use of **8** afforded **2c** in better yield than that of **6** (runs 7-9).

Table 2. Catalytic monoallylation of **1b,c**.^a

run	1,2-diol	catalyst	Yield (%)	
			2	3
1		4	35 ^b	nd ^c
2		5	15 ^b	nd ^c
3		6	75 ^b	nd ^c
4	1b	7	70 ^b	nd ^c
5		8	64 ^b	nd ^c
6		4	12 ^d	nd ^c
7		5	4 ^d	nd ^c
8		6	61 ^d	nd ^c
9	1c	7	68 ^d	nd ^c
10		8	78 ^d	nd ^c

^a To a mixture of diol, K₂CO₃ (1.5 equiv), and catalyst (0.1 equiv) in DMF was added allyl bromide (2 equiv). The mixture was stirred for 38 h at rt. ^b Isolated yield. ^c Not detected. ^d Determined by GLC.

This result indicates that there is a suitable combination between diols and catalysts to achieve an efficient catalytic cycle. The best combination seems to be controlled by both acidity of diols and Lewis acids. In the case of using relatively weak Lewis acid such as **5**, the first and second steps could be slow, while possibly higher reactivity of resulting intermediate **Ba-c** would accelerate the third step (Scheme 1). On the other hand, relatively strong Lewis acid such as **6-8** would be favor for the first and second steps, while stabilized intermediate **Ba-c** may make the third step sluggish. Thus, suitable catalyst, which maximizes the overall reaction rate, would be determined depending on each diol's acidity. Diol **1a** has acidic hydroxyl groups that easily form a complex **Ba** with relatively weak Lewis acid **5**, which enhances the reaction rate for allylation. On the other hand, less acidic diol **1c** would be slow to form a complex **Bc**, thus needs strong Lewis acid **8** to achieve fast formation of **Bc**. Since the acidity of **1b** is considered to be located between **1a** and **1c**, the result that the best catalyst for allylation of **1b** is electron-rich boronic acid **6** seems to meet this.

Next, we examined the catalytic process for diols **1a-d** with various alkylating reagents (Eq. 3). Table 3 shows the results.

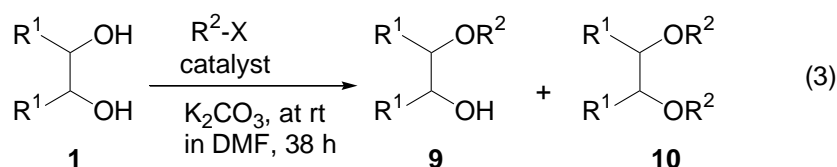
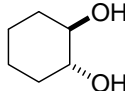


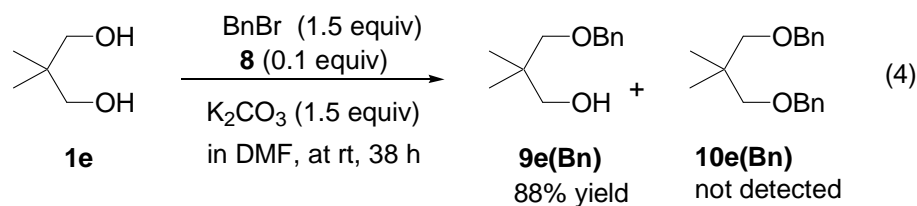
Table 3. Catalytic monoalkylation of 1,2-diols^a

run	diol	catalyst	R ² -X (equiv)	product (yield: %) ^b				
				9	10			
1	1a	5	MeI (10)	9a(Me)	65 ^b	10a(Me)	<1	
2	1a	5	BnBr (1.2)	9a(Bn)	79 ^b	10a(Bn)	<1	
3	1a	5	EtI (5)	9a(Et)	45 ^b	10a(Et)	<1	
4	1b	6	MeI (10)	9b(Me)	89 ^b	10b(Me)	nd ^c	
5	1b	6	BnBr (1.5)	9b(Bn)	64 ^b	10b(Bn)	nd ^c	
6	1c	8	BnBr (1.5)	9c(Bn)	84 ^b	10c(Bn)	nd ^c	
7 ^d	1c	8	BnBr (1.5)	9c(Bn)	99 ^b	10c(Bn)	nd ^c	
8 ^e	1c	8	EtI (5)	9c(Et)	79 ^f	10c(Et)	nd ^c	
9		8	BnBr (1.5)	9d(Bn)	25 ^b	10d(Bn)	nd ^c	
10 ^g	1d	8	BnBr (3)	9d(Bn)	91 ^b	10d(Bn)	1	

^a To a mixture of diol, K₂CO₃ (1.5 equiv), and catalyst (0.1 equiv) in DMF was added R²-X. The mixture was stirred for 38 h at rt. ^b Isolated yield. ^c Not detected. ^d MeCN containing 0.2 equiv of Et₄NBr was used instead of DMF. ^e 46 h of reaction time was applied. ^f Determined by GLC. ^g A mixture of toluene and 50% KOH containing 1 equiv of Et₄NBr was used instead of DMF-K₂CO₃.

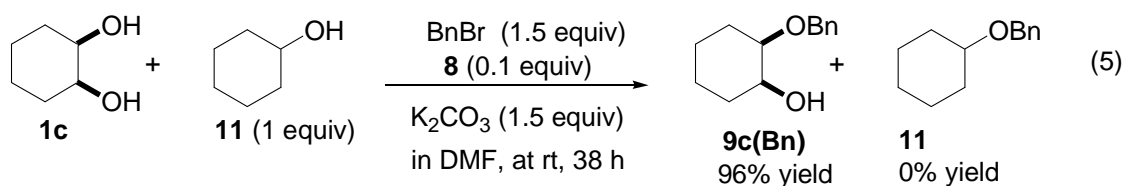
These alkylating reagents selectively afforded monoalkylated products **9a-d** in good to moderate yields. Use of excess amount of alkylating reagent was required because of its low reactivity. Even in cases where large excess amount of alkylating reagents were used, formation of corresponding dialkylated products **10a-d** were minute (runs 1,3,4,8). It was found that MeCN and Et₄NBr as a phase transfer catalyst improved the yield of **9c(Bn)** (run 5). Although *trans*-cyclohexane-1,2-diol **1d** afforded only poor yield (25%) of **9e(Bn)** under standard condition (run 9), the yield was significantly improved when a mixture of toluene and 50% KOH containing 1 equiv of Et₄NBr was used (run 10).

Moreover, the method was found to be applicable to monobenzylation of 1,3-diol **1d** (Eq. 4).



To demonstrate chemoselectivity **1c** and cyclohexanol (**11**) were subjected to this

method and only **1a** was monbenzylated to afford **9c(Bn)** in 96% yield (Eq. 5).



In conclusion, we have developed a new catalytic monoalkylation method for 1,2-diols. This method is convenient and can be widely applied, since it does not require a strong base such as NaH therefore tolerant to ester groups. Moreover, we have found that the choice of catalysts for monoalkylation of 1,2-diols depended on their acidity. The asymmetric version of monoalkylation is currently underway.

Acknowledgements

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References and notes

1. (a) Lee, G. H.; Choi, E. B.; Lee, E.; Pak, C. S. *J. Org. Chem.* **1994**, *59*, 1428-1443; (b) Guidry, E. N.; Cantrill, S. J.; Stoddart, J. F.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 2129-2132.
2. (a) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593-1596; (b) Mikami, T.; Asano, H.; Mitsunobu, O. *Chem. Lett.* **1987**, 2033-2036; (c) Takasu, M.; Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 1947-1950; (d) Barton, D. H. R.; Zhu, J. *Tetrahedron* **1992**, *48*, 8337-8346.
3. (a) Leznoff, C. C. *Acc. Chem. Res.* **1978**, *11*, 327-333; (b) Nishiguchi, T.; Kawamine, K.; Ohtsuka, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 153-156.
4. Kalinowski, H.-O.; Crass, G.; Seebach, D. *Chem. Ber.* **1981**, *114*, 477-487.
5. McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388-3390.
6. Bouzide, A.; Sauve, G. *Tetrahedron Lett.* **1997**, *38*, 5945.
7. (a) Nagashima, N.; Ohno, M. *Chem. Pharm. Bull.* **1991**, *39*, 1972-1982; (b) Scheufler, F.; Maier, M. E. *Synlett* **2001**, 1221-1224; (c) Schmidt, B.; Nave, S. *Adv. Synth. Catal.* **2007**, *349*, 215-230.
8. Oshima, K.; Kitazono, E.; Aoyama, Y. *Tetrahedron Lett.* **1997**, *38*, 5001-5004.
9. Jha, S. C.; Joshi, N. N. *J. Org. Chem.* **2002**, *67*, 3897-3899.
10. Petursson, S.; Webber, J. M. *Carbohydr. Res.* **1982**, *103*, 41-52.
11. De La Zerda, J.; Barak, G.; Sasson, Y. *Tetrahedron* **1989**, *45*, 1533-1536.
12. Bessodes, M.; Boukarim, C. *Synlett* **1996**, 1119-1120.

13. (a) Maki, T.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* **1998**, *39*, 5601-5604; (b) Iwasaki, F.; Maki, T.; Nakashima, W.; Onomura, O.; Matsumura, Y. *Org. Lett.* **1999**, *1*, 969-972; (c) Iwasaki, F.; Maki, T.; Onomura, O.; Nakashima, W.; Matsumura, Y. *J. Org. Chem.* **2000**, *65*, 996-1002; (d) Demizu, Y.; Kubo, Y.; Miyoshi, H.; Maki, T.; Matsumura, Y.; Moriyama, N.; Onomura, O. *Org. Lett.* **2008**, *10*, 5075-5077.
14. (a) Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. *J. Am. Chem. Soc.* **2003**, *125*, 2052-2053; (b) Matsumura, Y.; Maki, T.; Tsurumaki, K.; Onomura, O.; *Tetrahedron Lett.* **2004**, *45*, 9131-9134; (c) Matsumoto, K.; Mitsuda, m.; Ushijima, N.; Demizu, Y.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 8453-8456; (d) Demizu, Y.; Matsumoto, K.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2007**, *48*, 7605-7609.
15. Typical procedure for monoallylation of 1,2-diol; To a solution of **1a,b** (1 mmol) and catalyst (0.1 mmol) in DMF (2 mL) was added K_2CO_3 (1.5 mmol) and allyl bromide (2 mmol) at room temperature. After stirring for 38 h, the mixture was poured into water and extracted three portion of ethyl acetate. The organic layer was combined and dried over $MgSO_4$. After filtration, the organic portion was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography.