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Catalytic intermolecular carbon electrophile induced semipinacol rearrangement†

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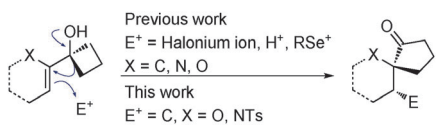
A catalytic intermolecular carbon electrophile induced semipinacol rearrangement was realized and the asymmetric version was also preliminarily accomplished with 92% and 82% ee. The complex tricyclic system architecture with four continuous stereogenic centers could be achieved from simple starting materials in a single step under mild conditions.

Intramolecular carbon electrophile induced semipinacol rearrangement (Prins-pinacol reaction) has been extensively studied as one of the powerful C–C bond forming reactions.[1,2] This tandem process initiated by the *in situ* formed stabilized carbocations is a practical protocol for the construction of complex molecular architectures through simple operation.[3] As a result, many elegant total syntheses of natural products have also been accomplished using this strategy as a key step.[4] Accordingly, the intermolecular ones are also important in terms of generating the complexity, diversity and especially chirality of the product from a simple prochiral substrate. However, due to the inherent low electrophilicity of carbon electrophiles compared with heteroatom ions, it was challenging for the semipinacol substrate (or motif) to survive under the harsh conditions such as stoichiometric strong Lewis acid (Scheme 1). Even though many formal intermolecular carbon electrophile induced (Prins-pinacol) semipinacol reactions have been disclosed through the preformation of hemiacetal,[5] examples of clear-cut intermolecular reaction are rarely reported and the catalytic asymmetric version of these transformations has not been reported.[6] Therefore, given the importance of forming multiple bonds and complex molecules in a single step without the need for the synthesis of complex substrates,[7] the intermolecular semipinacol rearrangements as a beneficial complement to the intramolecular ones are still highly desirable.



Scheme 1 Different electrophiles induced semipinacol rearrangement.

As a long standing research interest of our group, we have recently engaged in the enantioselective non-carbocation participated semipinacol rearrangement of the activated allylic alcohol such as enol ether and enamide which renders the alkene more basic and nucleophilic (X = N, O, Scheme 1).[8,9] Although the substrate is highly sensitive to acid as stated above,[10] based on these successful results, we envisioned that such a type of double bond might react with a carbon electrophile (E = C, Scheme 1) to effect an intermolecular semipinacol rearrangement. Herein, we wish to present our preliminary results on this subject.[2a,b]

Initially, **1a** and the electrophile ethyl glyoxalate **2a** were selected to verify the designed reaction (Table 1). When the non-protected substrate **1a** was subjected to the reaction conditions using DCM as solvent and $Cu(OTf)_2$ as a catalyst, only the direct semipinacol rearrangement product of **1a** was isolated leaving **2a** untouched (entry 1). We found that the protecting group of **1a** was critical for the performance of the reaction (entries 2–6). Thus **1b** with TBS protecting group was then attempted for screening of the reaction conditions (entries 2–15). When toluene was employed, the expected reaction took place which was followed by ketalization reaction to afford tricyclic compound **3b** in 52% yield with 51 : 1 dr (entry 2). However, under similar conditions in DCM, only trace amounts of **3a** could be detected (entry 3) and the result was even worse when the reaction was carried out in more polar solvent nitromethane (entry 4). Further screening showed that acetone was a promising solvent from which **3b** could be isolated in 42% yield but with a decreased dr of 10 : 1 (entry 5). The coordinating solvent THF was much better and the reaction proceeded readily to give **3b** in 64% yield and an excellent dr of >100 : 1 (entry 6).

The catalyst was also important for the performance of the reaction. For example, $(CuOTf)PhH_{1/2}$ could give a comparable yield of 51% albeit with a decreased dr of 43 : 1 (entry 7). While strong Lewis acid $Sc(OTf)_3$ or $In(OTf)_3$ could only give low yields (~10%) and poor dr (~1 : 1) (entries 8 and 9). On the other hand, the relatively weak Lewis acids such as $LaCl_3$, $ZnBr_2$, $MgBr_2$ and AgOTf

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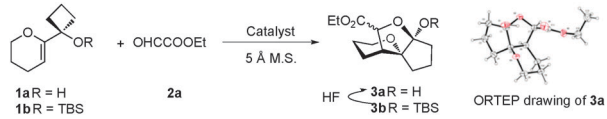
† Electronic supplementary information (ESI) available. CCDC 890030 (**3a**) and 890031 (**3hβ**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc38585f

Table 1 Optimization of the reaction conditions[a]



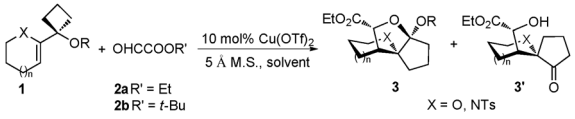
Entry	Solvent	Cat. (10 mol%)	Time (h)	Yield[b] (%)	dr[c]
1	DCM	$Cu(OTf)_2$	0.5	nd	—
2	Toluene	$Cu(OTf)_2$	2	52	51 : 1
3	DCM	$Cu(OTf)_2$	0.5	Trace	—
4	CH_3NO_2	$Cu(OTf)_2$	0.5	nd	—
5	Acetone	$Cu(OTf)_2$	0.5	42	10 : 1
6	THF	$Cu(OTf)_2$	4	64	>100 : 1
7	THF	$(CuOTf)PhH_{1/2}$	4	51	43 : 1
8	THF	$Sc(OTf)_3$	0.5	13	1.1 : 1
9	THF	$In(OTf)_3$	0.5	9	1.2 : 1
10	THF	$LaCl_3$	4	nd	—
11	THF	$ZnBr_2$	4	Trace	—
12	THF	$MgBr_2{\cdot}Et_2O$	4	nd	—
13	THF	AgOTf	4	nd	—
14[d]	THF	$Cu(OTf)_2$	4	79[f]	>100 : 1
15[d,e]	Acetone	$Cu(OTf)_2$	0.5	93	11 : 1

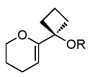
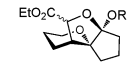
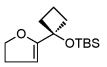
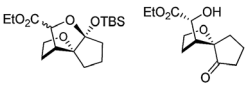
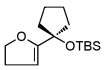
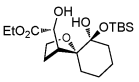
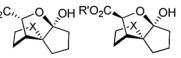
[a] Reaction conditions: **1b** (**1a** for entry 1) (0.1 mmol), **2** (0.2 mmol), catalyst (0.01 mmol), 100 mg 5 Å molecular sieves at rt. [b] Isolated yield. [c] dr of **α** : **β**, determined by ^{1}H NMR. [d] Addition of **1b** was performed using a syringe pump for 1 h. [e] The reaction was performed at −10 °C. [f] Yield of **3a** after being treated with HF (aq.).

were ineffective (entries 10–13). To further prevent the decomposition and direct semipinacol rearrangement of the substrate, slow addition of **1b** using a syringe pump was performed. Deprotected product **3a** along with **3b** was observed in this case. The reaction mixture finally gave **3a** in 79% yield without erosion of dr after being treated with aqueous HF (entry 14). Similarly, up to 93% yield could be gained with 11 : 1 dr at −10 °C in acetone (entry 15). These results above demonstrated the challenge of this tandem reaction which requires appropriate selection of each reaction parameter. It should be noted that other diastereomers were not detected in the above evaluation and the relative configuration of **3a** was unambiguously determined by X-ray crystallography.[11]

The substrate scope was then studied based on the above optimization (using $Cu(OTf)_2$ as a catalyst, THF or acetone as solvent, Table 2). As shown with **1c**, the variation of the protecting group from TBS to TMS gave a slightly increased yield of 85% and a lower dr of 5 : 1 (entry 2). Unlike the dihydropyran substrate **1b** and **1c**, the dihydrofuran substrate **1d** could also generate *cis* semipinacol rearrangement product **3c′** in 20% yield, which could not undergo further ketalization reaction (entry 3).[12] A total yield of 91% was obtained together with the normal product **3c** (71% yield). Cyclopentanol type substrate **1e**, which proved to be problematic in the Brønsted acid catalyzed asymmetric semipinacol rearrangement in our previous study,[7a] underwent smooth transformation at −10 °C to form hemiketal **3d** instead of the ketal counterpart in 42% yield and with relatively high dr (>10 : 1, entry 4) compared with substrates with cyclobutanol and cyclopropanol groups.[12] The dihydropyrrole counterparts **1g** and **1h** were also amenable to this protocol to give the products in good to excellent yields of 84%–96% (entries 5–7). The gram scale synthesis was performed with satisfactory results (entry 6), and a similar good result was obtained when *t*-butyl glyoxalate **2b** was used instead of **2a** as an electrophile (entry 7). In these cases (entries 5–7), the *cis*

Table 2 Substrate scope[a]



Entry	Substrate	Product[b] (dr)	Yield[c] (%)
1[e]			
	1b R = TBS	**3b** R = TBS (**α** : **β** 100 : 1)	79
2	**1c** R = TMS	**3a** R = H (**α** : **β** 5 : 1)	85
3			
	1d	**3c** (**α** : **β** 5 : 1) 71% **3c′** 20%	91
4[d]			
	1e	**3d** (**α** : **β** >10 : 1)	42
5	 X = NTs	 R′ =	
	1g	Et, **3eα** : **3e′** 78% (8 : 1), **3eβ** 16%	94
6	**1g** (1.0 g)	Et, **3eα** : **3e′** 81% (13 : 1), **3eβ** 15%	96
7	**1h**	^{t}Bu, **3fα** : **3f′** 67% (9 : 1), **3fβ** 17%	84

[a] **1** (0.2 mmol except for entry 6), **2a** (2.0 equiv., **2b** for entry 7), $Cu(OTf)_2$ (10 mol%), THF (2 mL) and 5 Å molecular sieves (200 mg) were stirred at rt. [b] Isolated yield, dr (**3α** : **3′** unless noted) confirmed by ^{1}H NMR. [c] Combined isolated yield. [d] Acetone was used instead of THF, the reaction was performed at −10 °C. [e] A syringe pump was used.

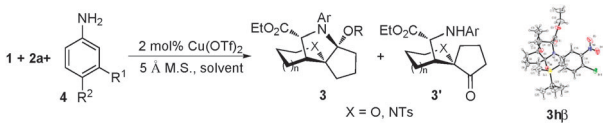
semipinacol rearrangement products (**3e′**–**3f′**) were also observed as minor isomers in 8 : 1, 13 : 1, 9 : 1 ratios, respectively, which were inseparable with **3eα** or **3fα**.

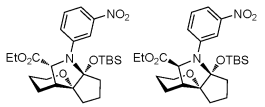
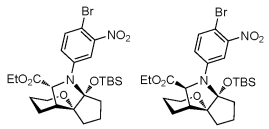
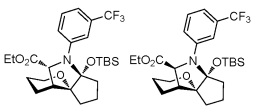
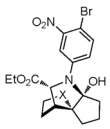
Subsequently, as shown in Table 3, the three-component reactions involving additional aromatic amines **4** were also tested using the procedure described in the footnote (also see ESI†). A good result was also obtained, giving **3g**–**3i** in 54–76% yield in acetone (entries 1–3).[13] However, only low dr values (**α** : **β**) could be gained (~1 : 1) for **3g**–**3i** and the *cis* semipinacol rearrangement products (**3g′**–**3i′**) also emerged (9 : 1, 11 : 1, 13 : 1 ratios with **3gα**–**3iα**). In contrast, when substrate **1g** was introduced with **4b** in THF instead of acetone, the major isomer was obtained in 83% yield together with other isomers which lack the stability to be verified (entry 4). The relative configuration of the minor diastereomer **3hβ** was also determined by X-ray crystallography which is consistent with the two component reaction.[11]

In order to facilitate this transformation's future applications, the asymmetric version of this tandem reaction was attempted (Scheme 2). Subsequently, **1g** was selected as the substrate and subjected to the catalytic asymmetric carbon electrophile induced semipinacol rearrangement reaction.[14] When the reaction was performed in the presence of 15 mol% $Cu(OTf)_2$ using (*S*,*S*)-*t*-BuBOX (15 mol%) as a ligand, the desired products **3eα** and **3eβ** could also be obtained in respective 79%, 20% yield and 91% , 82% ee, indicating the efficiency of the enantioselective reaction.[15]

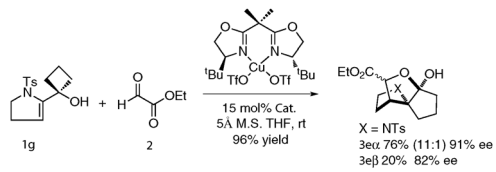
In conclusion, the catalytic intermolecular carbon electrophile induced semipinacol rearrangement was realized. The

Table 3 Three component reactions[a]



Entry	Substrate	Product[b] (dr)	Yield[c] (%)
1	**1b** **4a** (R^1 = NO_2 R^2 = H)	 **3gα : 3g′** 40% (9 : 1), **3gβ** 36%	76
2	**1b** **4a** (R^1 = NO_2 R^2 = Br)	 **3hα : 3h′** 35% (11 : 1), **3hβ** 32%	67
3	**1b** **4c** (R^1 = CF_3 R^2 = H)	 **3iα : 3i′** 31% (13 : 1), **3iβ** 23%	54
4[d]	**1g** and **4b**	 X = NTs, **3j**	83

[a] To an oven dried Schlenk tube was added **2** (2.0 equiv.), 5 Å molecular sieves (1 g), aniline derivatives **4** (1.0 equiv.), $Cu(OTf)_2$ (2 mol%) and acetone (5 mL). Addition of **1b** (1.0 mmol in 5 mL acetone) to the system was then performed using a syringe pump for 1 h at room temperature. [b] Isolated yield, dr (**3α : 3′**) confirmed by ^{1}H NMR. [c] Combined isolated yield. [d] 0.2 mmol scale in THF with a 15 mol% catalyst, without using a syringe pump.



Scheme 2 Catalytic enantioselective intermolecular carbon electrophile induced semipinacol rearrangement.

complex tricyclic system architecture with four continuous stereogenic centers could be achieved from simple starting materials under mild conditions. The enantioselective version was also developed with excellent results. We believe that this reaction would find its extensive applications in organic synthesis. Further development and improvement of the reaction and its applications in total synthesis is currently underway.

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11 Crystallographic data for **3a**, **3h**β have been deposited at the Cambridge Crystallographic Data Centre (deposition no. CCDC 890030 (**3a**); 890031 (**3hβ**))†.
12 In our study, the *cis* semipinacol rearrangement product **3′** was detected as one isomer, for similar results see ref. 6.
13 Complex mixtures were observed in THF for entries 1–3, Table 3.
14 For selected examples of related asymmetric Prins and ene reactions, see: (*a*) H.-K. Luo, Y.-L. Woo, H. Schumann, C. Jacob, M. van Meurs, H.-Y. Yang and Y.-T. Tan, *Adv. Synth. Catal.*, 2010, **352**, 1356; (*b*) C. A. Mullen and M. R. Gagné, *Org. Lett.*, 2005, **8**, 665; (*c*) M. Kim, H. S. Jeong, C.-E. Yeom and B. M. Kim, *Tetrahedron: Asymmetry*, 2012, **23**, 1019; (*d*) S. Doherty, J. G. Knight and H. Mehdi-Zodeh, *Tetrahedron: Asymmetry*, 2012, **23**, 209; (*e*) K. Zheng, X. Liu, S. Qin, M. Xie, L. Lin, C. Hu and X. Feng, *J. Am. Chem. Soc.*, 2012, **134**, 17564.
15 The absolute configurations of the products were not verified, and Scheme 2 only shows the relative configurations of them.

