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Study on improved diastereoselectivity in photo-induced electron transfer pinacol coupling reactions of substituted acetophenones

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ABSTRACT

Novel diastereoselective photo-induced pinacol coupling reactions of acetophenones by using triethylamine and chiral tertiary amines as electron donating co-sensitizers were studied. Various influence factors including solvents, substituents, and chiral amines on both the diastereoselectivity and yield were examined. The diastereoselectivities were enhanced in supramolecular systems of cyclodextrins and zeolites. The best result of *dl*/*meso* up to 82:18 was obtained in combination use of chiral tertiary amine and β-CD.

1. Introduction

While thermal asymmetric synthesis has been successfully utilized for decades, the photochemical counterpart is still in its early stages. In recent years enormous efforts have been made to develop versatile methods in photo-induced asymmetric synthesis.[1,2] Such asymmetric photochemical reactions exhibit unique superiority in high energy, simplicity, and green chemistry as compared with conventional synthesis.[1a,9] The latest study has also shown that supramolecular systems such as modified cyclodextrins and zeolites have been employed in asymmetric photoreactions, which act as 'microreactors' and provide chiral space for interactions between the host and the guest.[1a,3–8] In addition, applications of chiral photosensitizers, chiral memory effect and absolute asymmetric photochemistry have also attracted considerable attention.[10–13]

1,2-Diols are important structural motifs found in many natural products and drugs such as taxol®, protease inhibitor, inositols, etc.[14] They have also been widely utilized in organic chemistry as chiral ligands and auxiliaries. Pinacol coupling of aldehydes or ketones is a well known method for synthesis of 1,2-diols.[15–17] However, asymmetric pinacol coupling reaction has remained a significant synthetic challenge. So far the major efforts have been focused on catalysis of chiral low-valent titanium and chromium complexes to achieve stereoselectivity. Good to excellent enantio- and diastereoselectivities have been reported by different groups.

The photo-induced pinacol coupling reaction has also been studied as a reliable and convenient method since 1900.[14] However, there have been only few reports regarding the stereoselectivity and limited progress has been made. Seebach and Daum[18] made early attempts to use a chiral amino ether to initiate photo-pinacol coupling of aromatic ketones, but the *dl*/*meso* ratio remained at a unsatisfactory level (~50:50). Therefore, there is still a great need to explore novel approaches for stereoselective photo-induced pinacol coupling reaction.

In this Letter an effective and diastereoselective photo-induced pinacol coupling of substituted acetophenones via electron transfer photosensitization using tertiary amines as electron donating co-sensitizers. The presence of cyclodextrins and zeolites also has influenced diastereoselectivity. Of these, the β-CD–acetophenone inclusion complex along with combination use of tertiary amine **9** gave the best result of *dl*/*meso* up to 82:18.

2. Photo-pinacol coupling reaction in solution

Upon irradiation of UV light and in the presence of triethylamine as electron donating co-sensitizer, acetophenone **1** underwent the pinacol coupling reaction in methanol to give pinacol **1′** in high yield (92%), but the diastereoselectivity was not satisfactory (*dl*/*meso* = 53:47). To improve the diastereoselectivity, optimization of the reaction conditions was studied including the solvent and substituent effects on the yield and diastereoselectivity. The reactions were carried out in nine solvents. The results showed that high yields remained in ~90% for most solvents used except moderate yields in THF and DMF. The product diastereoselectivity by measuring the ratio of *dl*/*meso* in various solvents showed a

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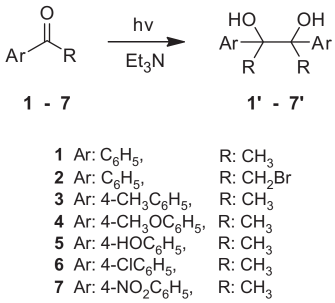
little change around 50:50. However, the para-substituents of benzene ring in acetophenones (**1**–**7**, see Scheme 1) had considerable influence on both the yield and ratio of *dl*/*meso*. It can be seen from Table 1 that high yields (>90%) remained for entries 1 and 3. The yield is extremely low (30%) for the methoxy substituent (entry 4). Surprisingly, almost no reaction was observed in the case of the hydroxy-substituent (entry 5). This is probably attributed to the strong inhibition effect of free radical scavengers like phenol on the formed ketyl radical anion of acetophenone, therefore, the coupling of the ketyl radical anion is totally suppressed.

An electron transfer (ET) mechanism for the title reaction with tertiary amine as shown in Scheme 2 is proposed. It is well established that photoreduction of ketones in the presence of amines led to ketyl radicals through photo-induced ET.[19] Excitation of acetophenone leads to its predominated triplet state, which is much stronger electron-accepting than its ground state. ET from the ground state of tertiary amine to the triplet of acetophenone generates the radical ion pair. The coupling and protonation of the ketyl radical anion lead to the pinacol formation, whereas tertiary amine radical cation undergoes deprotonization and coupling to give the diamine **8**. Evidence supporting the above ET mechanism showed that the coupling product of diamine **8** was detected by GC–MS. Besides, the experiments indicated that the yield drastically deceased to 10% with addition of equivalent amount of 1,4-dimethoxylbenzene (DMB), which was employed as an typical trapping agent of radical cation.

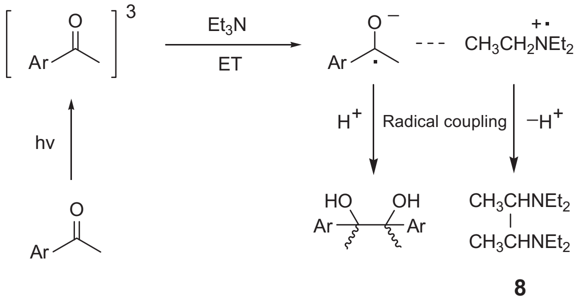


Scheme 1. Photo-induced pinacol coupling reaction of substituted acetophenones (**1**–**7**) with Et_3N.

Table 1
The substituent effect of acetophenones on photo-induced pinacol coupling with Et_3N in methanol[a],[20]

Entry	Ar	R	Yields (%)	*dl*/*meso*
1	C_6H_5	CH_3	92	53:47
2	C_6H_5	CH_2Br	75	52:48
3	4-$CH_3C_6H_5$	CH_3	99	65:35
4	4-$CH_3OC_6H_5$	CH_3	30	66:34
5	4-HOC_6H_5	CH_3	~0	–
6	4-ClC_6H_5	CH_3	58	63:37
7	4-$NO_2C_6H_5$	CH_3	50	67:33

[a] Molar ratio of substrate and Et_3N = 1:1.



Scheme 2. Proposed mechanism of the pinacol coupling reaction induced by tertiary amine.

3. Chiral tertiary amines as co-sensitizers

It is established that chiral amines were often used for chiral induction in asymmetric synthesis.[1a] For this purpose, five chiral tertiary amines (**9**–**13**) shown in Figure 1 were employed in this work.

The data in Table 2 indicate that only chiral *N*,*N*-dimethyl phenylethylamines **9**, **10** gave better results in both yields and ratios of *dl*/*meso*, whereas very low yields (<5%) were found with induction of **11**, **12,** and **13**. It is likely that large space of the chiral tertiary amines could not facilitate the coupling reaction because the amine donates an electron to acetophenone upon excitation to form the radical ion pair, where the amine radical cation should be close to the ketyl radical anion, hence the larger chiral amine might prohibit the coupling of the ketyl radical anion.

4. The coupling reaction of acetophenones in supramolecular systems

Cyclodextrins and zeolites were widely used as unique microreactors in many reactions due to their special cavities.[1a,3–8] Our experiments also demonstrated that those supramolecular systems apparently improved the diastereoselectivity.

The results showed that the cavity sizes of cyclodextrins had profound influence on both the reaction diastereoselectivity and the product yield. The photo-induced pinacol coupling of the inclusion complexes of α- and γ-CD with acetophenone displayed very low diastereoselectivity (*dl*/*meso* = 49.5–55) with moderate yields

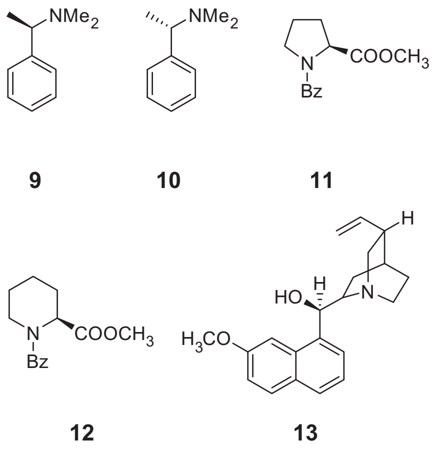


Figure 1. Chiral tertiary amines **9**–**13**.

Table 2
The photo-pinacol coupling of **1** induced by chiral tertiary amines in methanol

Co-sensitizer[a]		Yields (%)	*dl*/*meso*
Et_3N		92	53:47
(*R*)-(+)-*N*,*N*-Dimethyl-1-phenylethylamine	**9**	89	60:40
(*S*)-(−)-*N*,*N*-Dimethyl-1-phenylethylamine	**10**	85	56:44
N-Benzyl-L-proline methyl ester	**11**	5	–
N-Benzyl-L-nipecotic methyl ester	**12**	5	–
Quinine	**13**	3	–

[a] Molar ratio of amine and **1** = 1:1.

Table 3
Combination influence of chiral amine and β-CD to the photoreaction in H_2O

Molar ratio of inclusion complex			Yields (%)	*dl*/*meso*
β-CD	Chiral amine **9**	Acetophenone		
1	0	**1**	79	68:32
1	0.5	**1**	81	71:29
1	1	**1**	85	82:18
2	1	**1**	80	79:21

Table 4
Enfluence of loading NaY zeolites on the reactions

Entry	The ratio of loaded compounds		Yields (%)	*dl*/*meso*
	Chiral amine **9**	Acetophenone		
1	0.5	1.0	69	67:33
2	1.0	1.0	70	69:31
3	2.0	1.0	77	69:31
4	5.0	1.0	80	70:30

(60–78%), whereas β-CD gave much better results. As shown in Table 3, *dl*/*meso* ratio increased to 68:32 with the molar ratio of β-CD and acetophenone as 1:1. Hence, the data indicate that the main function of β-CD is its special confined spaces, where the movement (rotation, vibration, etc.) of substrate (excited state, reactive intermediate) is restricted, causing diastereoselectivity.

Interestingly, irradiation of the β-CD–acetophenone inclusion complex in the presence of chiral tertiary amine **9** provided the best result. The *dl*/*meso* ratio was improved up to 82:18 when the molar ratio of β-CD, chiral amine, and acetophenone was 1:1:1. The coupling product mixture was further analyzed by HPLC by a chiral column chromatography (CHIRALCEL AD-H) and 30% ee was obtained. To the best of our knowledge, this result has not been reported in the photo-induced pinacol coupling reaction up to date.

The supramolecular channels and windows of zeolites are another powerful tool in asymmetric photochemical reactions by their recognition ability. The NaY zeolites were known to induce diastereoselectivity.[1a] The photo-induced pinacol coupling reaction of acetophenone loaded on NaY zeolites was studied, and the results were shown in Table 4. It showed that increasing the molar ratio of chiral amine **9**, slightly improved the *dl*/*meso* ratio from 65:35 to 70:30 while the yields remained in 70–80%.

In summary, a novel and facile electron transfer photo-induced pinacol coupling reaction of acetophenones in various systems was developed. We have demonstrated that the substituents of acetophenones and chiral tertiary amines had considerable influence on both the yield and the ratio of *dl*/*meso*. The reactions in β-CD and NaY zeolites improved the diastereoselectivity as well. The best result of *dl*/*meso* (82:18) was obtained when the title reaction was carried out in β-CD with combination of the chiral tertiary amine **9**. Further study on the reaction scope and stereoselectivity is under way.

Acknowledgment

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References and notes

1. (a) Inoue, Y.; Ramavurthy, V. *Chiral Photochemistry*; New York: Marcel Dekker Press, 2004; (b) Inoue, Y. *Chem. Rev.* **1992**, *92*, 741–770; (c) Renaud, P.; Leong, P. *Science* **2008**, *322*, 55–56.
2. Lattanzi, A.; Scettri, A. *Curr. Org. Chem.* **2004**, *8*, 607–621.
3. Matsushita, Y.; Ichimura, T.; Ohba, N.; Kumada, S.; Sakeda, K.; Suzuki, T.; Tanibata, H.; Murata, T. *Pure Appl. Chem.* **2007**, *79*, 1959–1968.
4. Rao, V. P.; Zimmtt, M. B.; Turro, N. J. *J. Photochem. Photobiol., A: Chem.* **1991**, *57*, 7–9.
5. Leibovitch, M.; Olovsson, G.; Sundarababu, G.; Ramamurthy, V.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1996**, *118*, 1219–1220.
6. (a) Joy, A.; Uppili, S.; Netherton, M. R.; Scheffer, J. R.; Ramamurthy, V. *J. Am. Chem. Soc.* **2000**, *122*, 728–729; (b) Shailaja, J.; Keith, J. P.; Ramamurthy, V. *Org. Lett.* **2000**, *2*, 937–940; (c) Lu, F. F.; Wu, L. Z.; Zhang, L. P.; Tung, C. H.; Zheng, L. Q. *Youji Huaxue* **2006**, *26*, 599–609.
7. Toda, F.; Tanaka, K. *Chem. Commun.* **1986**, 1429–1430.
8. Nakamura, A.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 966–972.
9. Koodanjeri, S.; Ramamurthy, V. *Tetrahedron Lett.* **2002**, *43*, 9229–9232.
10. Scheffer, J. R.; Xia, W. *Top. Curr. Chem.* **2005**, *254*, 233–262.
11. Sakamoto, M. *J. Photochem. Photobiol., C: Photochem. Rev.* **2006**, *7*, 183–196.
12. Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1–16.
13. Griesbeck, A. G.; Uwe, J. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3147–3154.
14. (a) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630–634; (b) Mukaiyama, T.; Ogawa, Y.; Kuroda, K.; Matsuo, J. *Chem. Lett.* **2004**, *33*, 1412–1413; (c) Gracia, I. S.; Dietrich, H.; Bobo, S.; Chiara, J. L. *J. Org. Chem.* **1998**, *63*, 5883–5889; (d) Mühlman, A.; Lindberg, J.; Classon, B.; Unge, T.; Hallberg, A.; Samuelsson, B. *J. Med. Chem.* **2001**, *44*, 3407–3416.
15. Chatterjee, A.; Joshi, N. N. *Tetrahedron* **2006**, *62*, 12137–12158.
16. McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708–4709.
17. Hirao, T.; Hatano, B.; Imamoto, Y.; Ogawa, A. *J. Org. Chem.* **1999**, *64*, 7665–7667.
18. Seebach, D.; Daum, H. *J. Am. Chem. Soc.* **1971**, *93*, 2795–2796.
19. (a) Cossy, J.; Belotti, D. *Tetrahedron* **2006**, *62*, 6459–6470; (b) *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; New York: Plenum Press, 1984. Chapter 3.
20. *Typical experimental procedure*: (a) Procedure of the coupling reactions of acetophenone in solvent: Triethylamine (0.1 g, 1 mmol) was added to a solution of acetophenone (0.12 g, 1 mmol) in methanol (50 mL) in a sealed Pyrex-glass tube. The solution was purged with nitrogen bubbling for 30 min. The solution was irradiated under a 500 W medium pressure mercury lamp for 6 h. The reaction was monitored by TLC. After removal of solvent, 30 mL of ethyl acetate was added to the residue, washed with 5 mL of 10% HCl, saturated aqueous solutions of $NaHCO_3$ and NaCl for three times, respectively. The organic layer of solution was dried with anhydrous sodium sulfate and the solvent was evaporated. The sample mixture was isolated on silica gel column with elution of petroleum ether–ethyl acetate (4:1) to give of the coupling product **1′** (0.11 g, 92%). The ratios of dl/meso of the product were determined to be 53:47 by HPLC. ^{1}H NMR δ = 1.49 (s, 6H, CH_3, dl), 1.58 (s, 6H, CH_3, meso), 2.36 (s, 2H, OH, meso), 2.67 (s, 2H, OH, dl), 7.18–7.16 (m, 10H, PhH); ESIMS: *m*/*z* 265 $[M+Na]^+$ (100%).
    (b) Procedure of the coupling reactions of acetophenone in β-CD: Preparation of the inclusion complex of substrates in β-CD: 1.13 g (1 mmol) of β-CD was dissolved in 50 mL of water with stirring. When 0.12 g of acetophenone (1 mmol) and 0.15 g of **9** (1 mmol) were added to the solution, white precipitate appeared immediately. The mixture was heated until the solution became clear, the heating was maintained for 6 h. The solution was cooled and the formed white solid was filtrated, washed with *n*-hexane, and dried. The suspended solution of the above inclusion complex in 100 mL of water was transferred to a sealed Pyrex-glass tube. The solution was purged with nitrogen bubbling for 30 min and irradiated under a 500 W medium pressure mercury lamp for 6 h. After completion of the reaction, the solution was extracted with 20 mL of ethyl acetate. The organic layer was washed with saturated aqueous solutions of $NaHCO_3$ and NaCl for three times, respectively, and dried with anhydrous sodium sulfate. After removal of solvent, the residue was purified on a silica gel column with elution of petroleum ether–ethyl acetate (4:1) to give the coupling product **1′** (0.106 g, 85%). The ratios of dl/meso of the product were determined to be 82:18 by HPLC. Compound **1′** was further analyzed by HPLC on a chiral column (CHIRALCEL AD-H) and 30% ee was obtained.