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Insights into the General and Efficient Cross McMurry Reactions between Ketones

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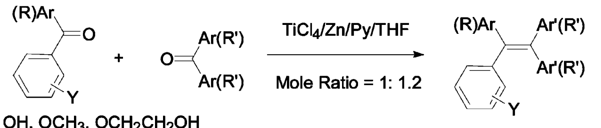

Y = OH, OCH_3, OCH_2CH_2OH
NH_2, NR_2, CH_2NR_2, etc.

isolated yield up to 94%

The selective cross McMurry couplings of diaryl or aryl ketones with various substituted ketones were achieved in 53−94% isolated yields. It is believed that the strong affinity of the substituents to the low-valent titanium surface plays an important role in regards to moderating selectivity. Through the introduction of such substituents followed by their removal post McMurry coupling, structurally similar ketones can be effectively cross-coupled.

The reductive coupling of carbonyl compounds to produce olefins through low valent titanium, known as the McMurry reaction,[1] has acquired great importance in organic synthesis. The broad interest in the reaction is expressed by a number of reviews outlining the synthetic applications and mechanism.[2] The couplings are particularly prominent in (a) preparations of sterically hindered alkenes through homocouplings and (b) construction of cycloalkenes with ring sizes ranging from 3 to 72 via intramolecular couplings.[3] The utility of this coupling reaction is highlighted as the key step in numerous syntheses of natural products.[4]

There are, however, remarkably few recorded examples of the cross McMurry couplings between two different carbonyl compounds. It is generally believed that this kind of cross coupling will generate a roughly statistical mixture of the possible coupling products. For synthetic purposes, such mixed couplings are useful when conducted with one component in excess or when the products are easily separable.[5,6] An exception to this rule exists when one of the carbonyl partners is a diarylketone. McMurry found that the cross-coupled products predominated if a diaryl ketone was coupled with an equimolar amount of aryl, aliphatic ketones or aldehydes.[6] McMurry also described the mechanistic basis for selectivity by postulating that the diaryl ketone first rapidly formed a dianion quantatively and then added to the saturated ketone. This type of cross coupling has already been used as the key step in the synthesis of the antitumor agent tamoxifen,[7] its analogues,[7] and the antihistamine drug loratadine.[8]

The few successful cross McMurry reactions were significantly dependent upon the structural differences between the two reactants, namely, (a) molecular weight allowing for products to be more separable and (b) reduction potential as diaryl ketones formed a dianion rapidly and quantatively. Obviously such strict structural requirements have limited the scope of the cross McMurry couplings. For this reason, other types of cross couplings such as diaryl ketones with diaryl ketones, aryl ketones with aryl ketones, and aryl ketones with aliphatic ketones remain a challenge. In this paper we report the results of our study on these cross couplings.

Our research is based on the premise that the coupling reaction occurs on the surface of the titanium and the difference of the affinity of reactants to the titanium surface should affect the outcome. To test this premise, we first chose two homocouplings and two mixed couplings: homocoupling of benzophenone (**1a**); homocoupling of 4, 4′-dimorpholinylbenzophenone (**1b**); cross coupling of **1a** with **1c** and cross coupling of **1a** with **1b** (Table 1, entries 1−4). The reactions were carried out using the $TiCl_4$−Zn−Py system.[7] For the cross couplings, the two carbonyl compounds were charged in equimolar amounts. It was observed that in the presence of the morpholinyl groups, both the homo- and cross couplings were remarkably retarded. Their cross reaction (entry 6) resulted in a selective cross coupling with an isolated yield of 56%. On the contrary, the coupling of **1a** and **1c** (entry 3) resulted in a nearly statistical mixture of the possible products. These results indicate that the morpholinyl group significantly influences the reductive coupling and enhances the selective cross coupling over homocoupling. In light of the more rapid consumption of **1a** during the reaction, the mole ratio of **1a** to **1b** was raised from 1:1 to 1.2: 1. As a result, the isolated yield of the cross-coupling product increased to 73% (Table 1, entry 7). Encouraged by these results, we carried out a variety of cross couplings between **1a** and **1b**−

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[1] (a) McMurry, J. E.; Felming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708. (b) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041.

[2] (a) Ephritikhine, M. *Chem. Commun.* **1998**, 2549. (b) Furstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2442. (c) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. (d) Lenoir, D. *Synthesis* **1989**, 883. (e) Kahn, B. E.; Rieke, R. D. *Chem. Rev.* **1988**, *88*, 733.

[3] (a) For the construction of 36-membered cyclic compounds, see Eguchi, T.; Terachi, T.; Kakinuma, K. *Chem. Commun.* **1994**, 137. (b) For 72-membered cyclic compounds, see Eguchi, T.; Ibaragi, K.; Kakinuma, K. *J. Org. Chem.* **1998**, *63*, 2689.

[4] Furstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2445.

[5] (a) Reddy, S. M.; Duraisamy, M.; Walborsky, H. M. *J. Org. Chem.* **1986**, *51*, 2361. (b) Paquette, L. A.; Yan, T.-H.; Wells, G. J. *J. Org. Chem.* **1984**, *49*, 3610.

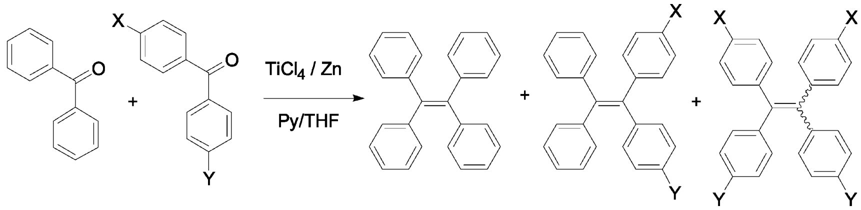
[6] McMurry, J. E.; Krepski, L. R. *J. Org. Chem.* **1976**, *41*, 3929.

[7] (a) Castedo, L.; Saa, J. M.; Suau, R.; Tojo, G. *Tetrahedron Lett*, **1983**, *24*, 5419. (b) Gauthier, S.; Mailhot, J.; Labrie, F. *J. Org. Chem.* **1996**, *61*, 3890. (c) Meegan, M. J.; Hughes, R. B.; Lloyd, D. G.; Williams, D. C.; Zisterer, D. M. *J. Med. Chem.* **2001**, *44*, 1072. (d) Detsi, A.; Koufaki, M.; Calogeropoulou, T. *J. Org. Chem.* **2002**, *67*, 4608. (e) Yu, D. D.; Forman, B. M. *J. Org. Chem.* **2003**, *68*, 9489. (f) Top, S.; Vessie, A.; Leclercq, G.; Quivy, J.; Tang, J.; Vaissermann, J.; Huche, M.; Jaouen, G. *Chem.*−*Eur. J.* **2003**, *9*, 5223. (g) Uddin, J.; Rao, P. N. P.; Knaus, E. E. *Synlett* **2004**, 513. (h) Pigeon, P.; Top, S.; Vessieres, A.; Huche, M.; Hillard, E. A.; Salomon, E.; Jaouen, G. *J. Med. Chem.* **2005**, *48*, 2814.

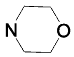
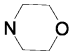
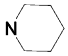
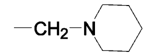
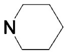
[8] (a) Alberto, S.; Pelayo, C.; Gloria, R.; Bosch, Onrubia, J.; Carmen, M. U.S. Patent 6084100, 2000. (b) Jackson, W. P. WO 9838166, 1998.

10.1021/jo061644d CCC: \$33.50

TABLE 1. Cross McMurry Reactions between Benzophenone and Diaryl Ketones



1a **1b-1q** **2aa** **2ab-2aq** **2bb-2qq**

Entry		Ketones	Ti (Eq)	Time[a] (h)	Yield (%)		
					2aa	**2ab~2aq**	**2bb ~2qq**
1	**1a**	**1a**	5	6	92(**2aa**)	-	-
2	**1b**	**1b:** X = Y = 	5	34	-	-	90(**2bb**)
3	**1a**	**1c**: X=H; Y=CH_3	5[b]	6	28[c]	44[c](**2ac**)	28[c]
4	**1a**	**1d** X = H; Y = Br	5[b]	5	30[c]	39[c]	30[c]
5	**1a**	**1e**: X = Y = CH_3	5[b]	6	32[c]	35[c]	33[c]
6	**1a**	**1b**	5[b]	36	17[b]	56[b](**2ab**)	17[b]
7	**1a**	**1b**	2	40	16	**64(2ab)**	11
	1a	**1b**	4	34	14	**70(2ab)**	8
	1a	**1b**	5	34	13	**73(2ab)**	8
	1a	**1b**	8	30	15	**72(2ab)**	9
	1a	**1b**	15	5	28	**36(2ab)**	27
8	**1a**	**1f**: X = H; Y = 	5	16	16	**62(2af)**	13
9	**1a**	**1g**: X = H; Y = 	5	36	20	**53(2ag)**	16
10	**1a**	**1h**: X = H; Y = 	5	38	21	**52(2ah)**	15
11	**1a**	**1i**: X = Y = 	5	36	15	**65(2ai)**	11
12	**1a**	**1j**: X = H; Y= OH	5	32	14	**66(2aj)**	10
13	**1a**	**1k**: X = Y = OH	5	36	14	**69(2ak)**	10
14	**1a**	**1l**: X= H; Y = OCH_3			16	**62(2al)**	12
15	**1a**	**1m**: X = Y = OCH_3	5	34	17	**59(2am)**	13
16	**1a**	**1n**:X=H;Y= OCH_2CH_2OH	5	30	17	**60(2an)**	14
17	**1a**	**1o**: X = Y = OCH_2CH_2O -CH_2CH_2OH	5	38	4	**89(2ao)**	3
18	**1a**	**1p**: X= H; Y = NH_2	5	13	10	**80(2ap)**	7
19	**1a**	**1q:** X= H; Y= CH_2NHPh	5	15	12	**68(2aq)**	9

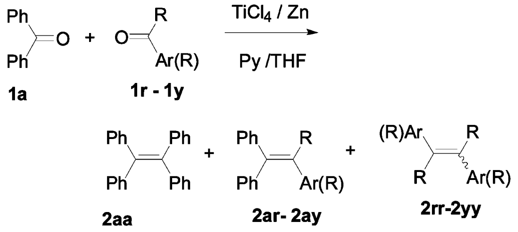
[a] The cross couplings were determined to be complete when **1a** was consumed, the hours were the whole reaction time after the homocouplings of **1b**−**q** were completed. [b] In these cases, the mole ratios of **1a** to **1b**−**e** were 1:1; in other cases the ratios of **1a** to **1b**, **1f**−**q** were 1.2:1. [c] The yields were obtained by GC analysis.

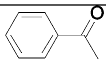
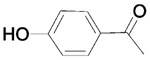
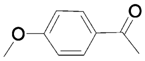
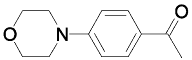
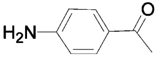
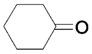
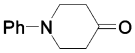
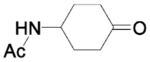
p. The generality with respect to the substituents was also established. The results are summarized in Table 1.

It was observed that a series of nitrogen or oxygen-containing substituents such as −OH, −OMe, −OCH_2CH_2OH, −$OCH_2CH_2OCH_2CH_2OH$, −NH_2, −NR_2, CH_2NHPh, and CH_2NR_2 decelerated the reaction and enhanced the selectivity of the cross coupling over the homocoupling reaction. In contrast, −CH_3 or −Br substituents did not display such effects (Table 1, entries 3−5). Polar substitutents such as −NH_2, −OH, −$OCH_2CH_2OCH_2CH_2OH$, and morpholinyl were more effective in this regard (Table 1, entries 7, 8, 12, 13, 17−19). The presence of two such substituents somewhat improved the cross coupling relative to one group as shown by comparing entry 7 with 8, 12 with 13, and 9 with 11 (Table 1).

It appears that these substituents affect the outcome of this reaction through their strong affinity to the surface of the titanium, rather than through altering the reduction potential or electronic density of the carbonyl moiety. This is exemplified by comparing entries 9 with 10 and 18 with 19 (Table 1). Experiments on the influence of the amount of low-valent titanium (Table 1, entry 7) indicated that 4−8 equiv of titanium were sufficient for the reaction to occur effectively. However, when the equivalents of titanium to **1b** were raised to 15:1, the mixed coupling proceeded rapidly and gave a roughly statistical mixture of three products. In view of the above-mentioned result, it is hypothesized that the selectivity of the cross couplings is influenced by the strong affinity of the substituents to the surface of titanium. We postulate that this interaction deactivates the titanium and decelerates the reaction. The homocoupling of **1a** is thus slowed. With the higher concentration of **1b**−**q**,

TABLE 2. Cross McMurry Reactions between Diary Ketones and Aryl Ketones or Aliphatic Ketones[a]



Entry	Ketone (1r-1y)	Yield (%)		
		2aa	2ar-2ay	2rr-2yy
1	**1r**: 	12	65	13
2	**1s:** 	13	71 (**2as**)	7
3	**1t:** 	4	92 (**2at**)	2
4	**1u:** 	3	94 (**2au**)	1.4
5	**1v:** 	12	80 (**2au**)	5
6	**1w:** 	2 (19)[b]	78 (78)[b]	10 (6)[b]
7	**1x:** 	5	92.5 (**2ax**)	0.5
8	**1y:** 	4	90.5 (**2ay**)	2

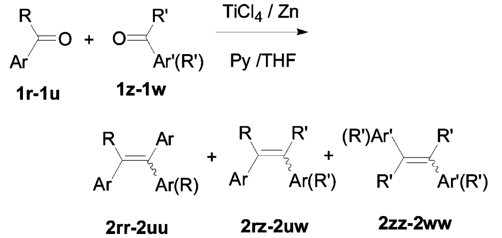
[a] The mole ratios of **1a** to **1r**−**y** were 1.2:1. [b] The yields in the parentheses were reported by J. E. McMurry in ref 6.

presumably on the titanium surface, the selectivity of the cross coupling was enhanced accordingly. When the amount of titanium was substantially excessive, this effect was minimized, and the couplings proceeded statistically.

We performed an additional series of cross couplings between diaryl ketones and aryl and aliphatic ketones. The results are presented in Table 2. As reported by McMurry,[6] this type of coupling predominantly generated the cross-coupling products even without the above-mentioned cross- coupling-enhancing substituents (Table 2, entries 1 and 6). However, the introduction of these groups such as −OH, −OMe, $-NH_2$, and morpholinyl substantially improved the yields of cross couplings (up to 94%, Table 2). This in turn, facilitated the isolation of the products.

The cross couplings of aryl ketones with aryl and aliphatic ketones were also investigated (Table 3). Not surprisingly, the reactions resulted in inseparable and nearly statistical mixtures of the possible products in the absence of the aforementioned substituents (Table 3, entries 1 and 6). The effect of substituents such as OH, OMe, NH_2, and morpholinyl was examined for the cross couplings of aryl ketones **1r** with **1s**−**u** (Table 3, entries 2−5) and aryl ketones **1s**−**u** with cyclohexanone (**1w**) (Table 3, entries 7−9). The desired cross-coupling products were obtained in 58−76.6% isolated yields. It should be noted that the couplings between aryl and aliphatic ketones occurred without selectivity when they were conducted with 5 equiv of low-valent titanium (Table 3, entry 7). The selective cross couplings were achieved using 2 equiv of low-valent titanium. At present, the cross couplings between two aliphatic ketones require further investigation. Our attempts to achieve the selective cross couplings between **1w** and **1x** and between **1w** and **1y** were unsuccessful.

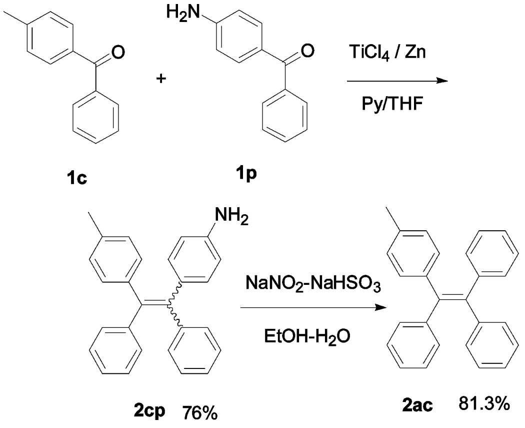
TABLE 3. Cross McMurry Reactions between Aryl Ketones and Aryl Ketones or Aliphatic Ketones [a]



entry	ketones		Ti equiv	yield (%)		
				2rr−**2uu**	**2rz**−**2uw**	**2zz**−**2ww**
1	**1r**	**1z**[b]	5.0	28[c]	41[c]	29[c]
2	**1r**	**1s**	5.0	18	58 (**2rs**)[d]	15
3	**1r**	**1t**	5.0	12	62.2 (**2rt**)[d]	12.5
4	**1r**	**1v**	5.0	16	60.2 (**2rv**)[d]	13
5	**1r**	**1u**	5.0	9	76.7 (**2ru**)[d]	6
6	**1r**	**1w**	5.0	27[c]	32[c]	29[c]
7	**1s**	**1w**	5.0	26	30 (**2sw**)	31
	1s	**1w**	2.0	8	70 (**2sw**)	13
8	**1t**	**1w**	2.0	9	69 (**2tw**)	14
9	**1u**	**1w**	2.0	14	60 (**2uw**)	17

[a] The mole ratios of **1r**, **1s**, **1t**, or **1u** to **1z**−**w** were 1.2:1. [b] **1z**: 4-methyl acetophone. [c] The yields were obtained by GC analysis. [d] The products were isolated and charaterized as a mixture of (*Z*) and (*E*) isomers.

SCHEME 1. Preparation of 2ac via Cross McMurry Coupling



Under standard conditions, structurally similar ketones such as **1a** and **1c** cannot be selectively cross coupled and their products are often difficult to purify. In light of the above results described in this paper, such ketones can be effectively cross coupled by utilizing the effects of substituents. Removal of the directing group would then provide the desired product (e.g., amino group as outlined Scheme 1). This provides a convenient and effective synthetic strategy for alkenes that were previously difficult to synthesize or inaccessible through McMurry couplings.

In conclusion, we have developed a novel general methodology to accomplish efficient cross McMurry reactions between two different ketones. This procedure significantly extends the scope of the McMurry reaction and enhances its utility as a powerful tool for C−C bond formation.

Experimental Section

General Procedure for Cross McMurry Reactions. Under an Ar atmosphere, a four-necked flask equipped with a magnetic stirrer was charged with zinc powder (1.6 g, 24 mmol) and 40 mL THF. The mixture was cooled to −5 to 0 °C, and $TiCl_4$ (1.3 mL, 12 mmol) was slowly added by a syringe with the temperature kept under 10 °C. The suspending mixture was warmed to room temperature and stirred for 0.5 h, then heated at reflux for 2.5 h. The mixture was again cooled to −5 to 0 °C, charged with pyridine (0.5 mL, 6 mmol) and stirred for 10 min. The solution of two carbonyl compounds [in 1:1 to 1:1.2 mole ratio (as illustrated in Tables 1, 2 and 3), 2.4 mmol (as illustrated in Tables 1, 2 and 3)] in 15 mL THF was added slowly. After addition, the reaction mixture was heated at reflux until the carbonyl compounds were consumed (monitored by TLC). The reaction was quenched with 10% K_2CO_3 aqueous solution and taken up with CH_2Cl_2. The organic layer was collected and concentrated. The crude material was purified by flash chromatography to give the desired products.

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Supporting Information Available: Typical experimental procedures and characterization data for **2bb** and 23 unknown cross-coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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