ORGANIC LETTERS

2011
Vol. 13, No. 2
176−179

Cross-Coupling Reactions of Two Different Activated Alkenes through Tetrabutylammonium Fluoride (TBAF) Promoted Deprotonation/Activation Strategy: A Regioselective Construction of Quaternary Carbon Centers

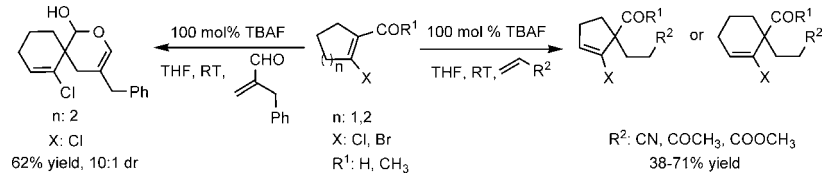
Jing-Li Zhang and Yue-Fa Gong*

Department of Chemistry, Huazhong University of Science and Technology, 1037 Luoyu Road, Wuhan, 430074, China

gongyf@mail.hust.edu.cn

Received September 8, 2010

ABSTRACT



A novel TBAF-promoted intermolecular crossed-conjugate addition has been developed. For a range of cyclic β-halo-α,β-unsaturated carbonyl compounds, the vinylogous enolates generated by deprotonation at the γ-position preferentially reacted with Michael acceptors at the α-position to deliver cross-coupling products in good yields.

Carbon−carbon bond formation is of significant importance in organic synthesis, with much research focused on discovering new, high efficiency, and selective reactions. Among many synthons for the formation of new C−C bonds, the electron-withdrawing group (EWG) activated alkene is considered one of the most fundamental building blocks in the construction of organic molecules. Its great reaction mode is the long-known conjugate 1,4-addition (Michael addition). Another important reaction of EWG-activated alkenes is the Lewis base promoted Morita−Baylis−Hillman (MBH) reaction, which merges the concepts of conjugate addition and carbanionic nucleophilic addition.[1] In addition to the MBH reaction, any coupling of one active alkene/latent enolate to a second Michael acceptor, creating a new C−C bond between the α-position of one activated alkene and the β-position of a second alkene under the influence of a nucleophilic catalyst is referred to as the Rauhut−Currier (RC) reaction (Scheme 1, Option 1).[2] The MBH or RC reaction, as a simple, efficient, and atom-economical process, which rapidly combines organic functionalities within a single manipulation, provides the densely functionalized products that serve as substrates for various attractive transformations.

In comparison to the MBH reaction, the RC reaction has received much less attention due to the low reactivity of substrates and difficulty in controlling the selectivity of a cross-coupling reaction. The main problem is that homocouplings compete under the reaction conditions, and the products which are electron-deficient alkenes as well are

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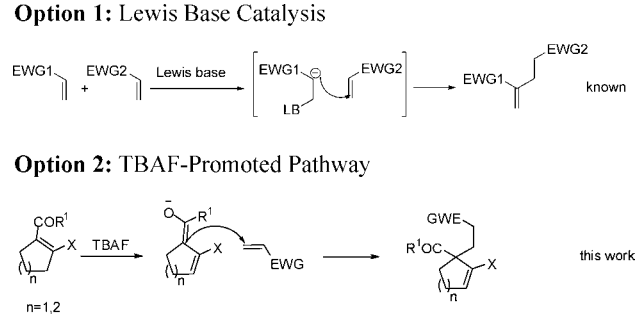
(2) (a) Rauhut, M. M.; Currier, H. U.S. Patent 3,074,999, 1963; Chem. Abstr. 1963,58,11224a. . (b) Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069–4084.

10.1021/ol1028332
Published on Web 12/10/2010

Scheme 1. Intermolecular Cross-Coupling Strategies of Electron-Deficient Alkenes

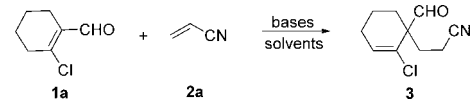


susceptible to polymerizations. In the past decade, significant progress has been made in the intramolecular RC reactions as well as in the enantioselective variants.[3]

Despite these advances in the intramolecular RC reactions, currently available synthetic applications of intermolecular RC reactions are sporadically documented in the literature.[4] For example, Scheidt made progress in the intermolecular RC reaction using silyloxyallenes catalyzed by a Lewis acid.[5] Ma reported an efficient, tertiary amine mediated cross-RC/acetalization of cyclic β-haloenals and β,γ-unsaturated α-ketoesters.[6] Recently, enantioselective intermolecular crossed-conjugate additions between nitroalkenes and α,β-enals through a dual activation were achieved by Shi's group.[7] Moreover, there was also a report of crossed intramolecular RC-type processes in the synthesis of the iridoid framework.[8] These notable works represent an attractive strategy in C−C bond construction. However, to date, there is still a lack of effective methodology for the intermolecular crossed-conjugate addition of different activated alkenes, which will produce highly functionalized products. On the other hand, the construction of a quaternary center is a significant challenge in the total synthesis of natural products.[9] One versatile access to all-carbon quaternary centers relies on the conjugated addition of enolates to acceptor-activated olefins. In this paper, we present an unprecedented tetrabutylammonium fluoride (TBAF) promoted tandem deprotonation/crossed-conjugate addition between cyclic β-halo-α,β-unsaturated carbonyl compounds and Michael acceptors, which affords a wide variety of 1,5-difunctional compounds containing an all-carbon quaternary center (Scheme 1, Option 2). This process is operationally simple as well as atom economic and minimizes the reaction time.

Based on our previous research, we speculated that TBAF would abstract a proton from cyclic β-chloro-enal at the γ-carbon to generate a carbanion intermediate or enolate and envisioned the carbanion intermediate could be intercepted by a Michael acceptor. With this hypothesis in mind, we initiated our investigation of cyclic β-chloro-enal **1a** with acrylonitrile **2a** in the presence of TBAF in THF. To our delight, such an intermolecular crossed-conjugate addition could indeed be accomplished. The reaction at room temperature proceeded smoothly within 3 min and gave a cross-coupling product **3** in 71% yield possessing an all-carbon quaternary center (Table 1, entry 1). However, no reaction

Table 1. Optimization of the Reaction Conditions[a]



entry	base (mol %)	solvent	temp (°C)	time[b]	yield (%)[c]
1	TBAF(100)	THF	rt	3 min	71
2	KF(100)	DMSO	rt	48 h	–
3	DBU(100)	THF	rt	48 h	–
4	TBAF(25)	THF	rt	24 h	26
5	TBAF(50)	THF	rt	12 min	43
6	TBAF(75)	THF	rt	6 min	65
7	TBAF(125)	THF	rt	2 min	61
8	TBAF(100)	DMF	rt	7 h	27
9	TBAF(100)	DMSO	rt	30 s	42
10	TBAF(100)	CH_3CN	rt	48 h	22
11	TBAF(100)	THF	20	5 min	69
12	TBAF(100)	THF	15	10 min	70

[a] **1a** (0.5 mmol), acrylonitrile (1.0 mmol), and Brønsted base in solvent (3.0 mL). [b] Reaction time was determined by TLC. [c] Isolated yields.

occurred with KF due to its poor solubility in the solvent (entry 2). Examination of other bases such as DBU (entry 3), Et_3N, DABCO, DMAP, imidazole, and PPh_3 revealed that none of them displays activities in this reaction. When 25 mol % of TBAF was employed in THF, the reaction proceeded slowly and afforded **3** in 26% yield after 24 h (entry 4). Upon changing the amount of TBAF to 50 mol %

(3) For recent intramolecular RC reaction, see: (a) Mergott, D. J.; Frank, S. A.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3157–3160. (b) Agapiou, K.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1737–1740. (c) Methot, J. L.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4223–4226. (d) Jellerichs, B. G.; Kong, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7758–7759. (e) Mergott, D. J.; Frank, S. A.; Roush, W. R. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11955–11959. (f) Wang, L. C.; Luis, A. L.; Agapiou, K.; Jang, H. Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402–2403. (g) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404–2405. (h) Aroyan, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 256–257. (i) Seidel, F.; Gladysz, J. A. *Synlett* **2007**, 986–988.

(4) (a) Hwu, J. R.; Hakimelahi, G. H.; Chou, C. T. *Tetrahedron Lett.* **1992**, *33*, 6469–6472. (b) Yin, Y. B.; Zhang, Q.; Li, J.; Sun, S. G.; Liu, Q. *Tetrahedron Lett.* **2006**, *47*, 6071–6074. (c) Dadwal, M.; Mohan, R.; Panda, D.; Mobin, S. M.; Namboothiri, I. N. N. *Chem. Commun.* **2006**, 338–340. (d) Sun, X. H.; Sengupta, S.; Petersen, J. L.; Wang, H.; Lewis, J. P.; Shi, X. D. *Org. Lett.* **2007**, *9*, 4495–4498.

(5) Reynolds, T. E.; Binkley, M. S.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 2449–2452.

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(7) Zhong, C.; Chen, Y. F.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 1279–1282.

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(9) For reviews, see: (a) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591–4597. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363–5367. (c) Trost, B. M.; Jiang, C. H. *Synthesis* **2006**, 369–396. (d) Cozzi, P. G.; Hilgarf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969–5994.

in THF, the reaction rate increased remarkably and the yield was improved to 43% (entry 5). When 75 mol % or 125 mol % of TBAF was used in THF, the yield of **3** increased to 65% after 6 min and 61% after 2 min, respectively (entries 6−7). Solvent screening gave THF as the most suitable solvent (entries 1, 8−10). Lowering the reaction temperature to 20 or 15 °C only led to a slightly extended reaction time without a decline in the yield (entries 11−12). The formation of cross-coupling product **3** indicated that the base directly abstracted a proton at the γ-position from **1a**, whereas the resulting vinylogous enolate preferentially reacted with **2a** at the α-position.

To study the reaction intensively, tetramethylammonium hydroxide pentahydrate (TMAH) and tetramethylammonium fluoride (TMAF), a "naked" fluoride of high basicity, were also employed as a Brønsted base in this reaction. Because of their poor solubility in THF, the same reaction was performed in DMSO. In the presence of 5 mol % of TMAH, **3** was obtained in 4% yield at a very slow rate (Table 2, entry 1). When the loading of TMAH was enhanced to 10 mol %, the reaction rate increased and the yield was improved (entry 2). Using 15 mol % of TMAH led to a considerable increase in the reaction rate and gave the product in a better yield (entry 3). However, upon employing 25 mol % of TMAH in this reaction, the yield of **3** fell to 25% (entry 4). Similar to TMAH, with the increase of TMAF concentration, the substrate consumption rate increased consistently, while the yield climbed and then declined (entries 5−8). The parallel experiments for TBAF in DMSO were also carried out, and the yield of **3** was much lower in DMSO than in THF (Table 2, entries 9−11). The results revealed that not only fluoride ion but also hydroxide ion are capable of deprotonating **1a**, but among the three bases, TBAF provides the best yield.

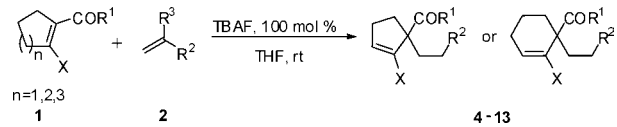
Table 2. Examination of TMAH and TMAF in the Reaction[a]

entry	base (mol %)	solvent	temp (°C)	time[b]	yield (%)[c]
1	TMAH(5)	DMSO	rt	48 h	4
2	TMAH(10)	DMSO	rt	24 h	22
3	TMAH(15)	DMSO	rt	10 min	34
4	TMAH(25)	DMSO	rt	30 s	25
5	TMAF(15)	DMSO	rt	13 h	18
6	TMAF(25)	DMSO	rt	5 min	28
7	TMAF(50)	DMSO	rt	1 min	35
8	TMAF(75)	DMSO	rt	30 s	18
9	TBAF(25)	DMSO	rt	11 h	20
10	TBAF(50)	DMSO	rt	7 min	37
11	TBAF(75)	DMSO	rt	2 min	46

[a] **1a** (0.5 mmol), acrylonitrile (1.0 mmol), and Brønsted base in solvent (3.0 mL). [b] Reaction time was determined by TLC. [c] Isolated yields.

The substrate scope of the TBAF-promoted cross-coupling reaction was then explored under the optimized conditions (Table 3). Interestingly, an unexpected spiro-3,4-dihydro-2*H*-pyran derivative was achieved by a tandem deprotonation/Michael addition/acetalization reaction process when 2-benzylacrylaldehyde **2b** was used as a Michael acceptor.

Table 3. Substrate Scope of the Cross-Coupling Reaction[a]



n=1,2,3

1 **2** **4 - 13**

entry	substrate	olefin	time (h)[b]	product	yield (%)[c]
1	**1a**	R^2 = CHO, R^3 = Bn **2b**	0.05	**4**	62
2	**1a**	R^2 = COMe, R^3 = H **2c**	0.08	**5**	67[d]
3	**1a**	R^2 = COOMe, R^3 = H **2d**	0.42	**6**	52[e]
4	**1b**	**2a**	0.05	**7**	68
5	**1c**	**2a**	0.08	**8**	59
6	**1d**	**2a**	48	-	-
7	**1e**	**2a**	0.33	**9**	63
8	**1f**	**2a**	0.33	**10**	60
9	**1g**	**2a**	0.67	**11**	56
10	**1h**	**2a**	1.5	**12**	58
11	**1i**	**2a**	12	**13**	38

[a] Unless otherwise indicated, reactions were carried out at room temperature, **1**/olefin = 1:2, and Brønsted base in solvent (3.0 mL). [b] Time for consuming **1**. [c] Isolated yields. [d] Reaction performed at 10 °C. [e] Reaction performed at 35 °C.

The ratio of the two diastereomers of **4** was determined by ^{1}H NMR analysis to be 10:1 (entry 1). Reaction of **1a** with methyl vinyl ketone (MVK) proceeded smoothly, and the corresponding cross-coupling product **5** was furnished in 67% yield (entry 2). In addition, methyl acrylate (MA), a less reactive Michael acceptor than MVK, could also react with **1a** at 35 °C, affording a moderate yield of the product **6** (entry 3). β-Nitrostyrene, however, failed to give the desired product due to its polymerization under the reaction conditions.

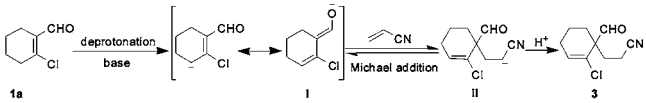
On the other hand, various cyclic β-halo-enals **1b**−**1g** were also investigated. The substituted variant 2-chloro-5-methylcyclohex-1-enecarbaldehyde **1b** was effective in furnishing the mixture of both diastereomers in a very short time, and the diastereoselective ratio of **7** was 1.9:1 (entry 4). The reactivity of the five-membered enal **1c** was comparative to that of **1a**, whereas the seven-membered enal **1d** was inactive

and no desired product was detected (entries 5−6). With respect to the halogen atom, not only chlorides but also bromides (entries 7−9) could be employed to give cross-coupling products **9**−**11** with a slower rate. Similarly, the diastereoselective ratio of the product **10** was 2.2:1. The compound **1h** gave the desired product in a modest yield (entry 10). Furthermore, cyclic β-haloenone **1i** also went well, albeit with lower yields and a longer time (entry 11).

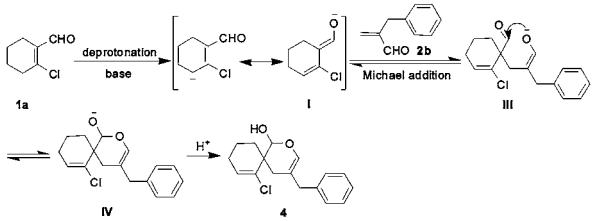
A plausible pathway **A** for this Brønsted base promoted crossed-Michael addition is illustrated in Scheme 2. We propose that the base abstracts a hydrogen atom directly from β-haloenal **1a** at the γ-position, and the vinylogous enolate **I** produced *in situ* preferentially reacts with a Michael acceptor at its α-position to afford another carbanion intermediate **II**. Subsequent protonation gives the cross-coupling product **3**. As for the formation of spiro-3,4-dihydro-2*H*-pyran **4**, an alternative pathway **B** for the tandem deprotonation/Michael addition/acetalization reaction is illustrated in Scheme 2. Deprotonation of enal **1a** provides vinylogous enolate **I**, subsequent intermocular Michael addition onto 2-benzylacrylaldehyde **2b** affords another enolate **III**, and the newly formed enolate proceeds intramolecular acetalization with the tethered aldehyde giving spirocyclic alkoxide **IV**. Finally, the protonation of intermediate **IV** generates hemiacetal **4**. Another conjugate addition of compound **1h** to the Michael acceptor is also shown in Scheme 2. The nonconjugated alkenyl ketone is easily deprotonated at the α-position to produce the vinylogous enolate **V**, the carbanionic intermediate adds to Michael acceptor yields intermediate **VI**, and the protonation of **VI** gives product **12**.

Scheme 2. Possible Reaction Pathways

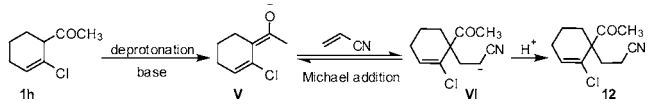
Pathway A: Base Promoted Crossed-Michael Addition



Pathway B: Base Promoted Tandem Deprotonation/Michael Addition/Acetalization Reaction

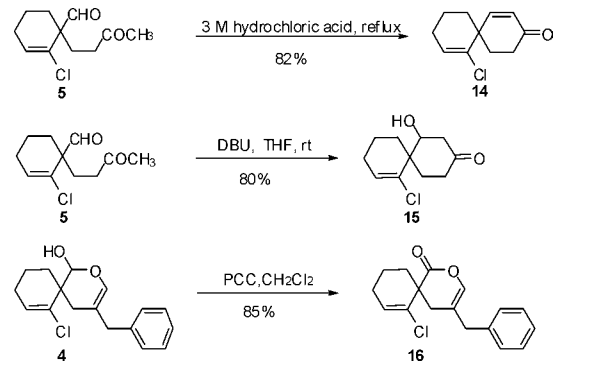


Pathway C: Base Promoted Michael Addition



The cycloaldolization reaction readily rendered the spiro cyclic enone **14** in 82% yield in an acidic medium (Scheme 3). In contrast, a DBU-mediated intramolecular aldol reaction of **5** led to spiro compound **15** as a single diastereomer in 80% yield. This transformation provided an effective and concise method to obtain the useful molecules containing a spiro structure. In addition, the lactone **16** was also easily achieved by oxidation of hemiacetal **4** with pyridinium chlorochromate (PCC) in 85% yield.

Scheme 3



In summary, we have developed a new Brønsted base promoted method for the intermolecular crossed-conjugate addition between two different activated alkenes under mild conditions. This method facilitates the construction of all-carbon quaternary centers and synthesis of spirocyclic compounds. Specifically, a functionalized spiro-2*H*-pyran derivative involving a quaternary carbon center and adjacent vinyl halogen group in the skeleton is readily synthesized from enal and an enal through a highly selective crossed-Michael addition. Moreover, the products with 1,5-difunctional groups are synthetically attractive and can be easily transformed into many other complex building blocks. Efforts are currently directed at further innovations in reaction scope and the development of enantioselective variants, and the results will be reported in due course.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (20872041). The Center of Analysis and Testing of HUST is thanked for characterization of new compounds.

Note Added after ASAP Publication. Scheme 2 contained errors in the version published ASAP December 10, 2010; the correct version reposted December 16, 2010.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1028332