ORGANIC LETTERS

2012
Vol. 14, No. 9
2354–2357

Lewis Base Promoted Intramolecular Acylcyanation of α-Substituted Activated Alkenes: Construction of Ketones Bearing β-Quaternary Carbon Centers

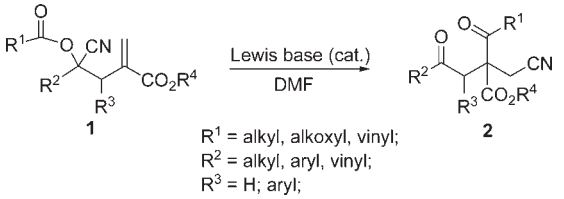
Zhe Zhuang, Jian-Ming Chen, Feng Pan, and Wei-Wei Liao*

Department of Organic Chemistry, College of Chemistry, Jilin University, 2699 Qianjin Street, Changchun 130012, China

wliao@jlu.edu.cn

Received March 26, 2012

ABSTRACT



A novel phosphine-promoted intramolecular acylcyanation of α-substituted activated alkenes has been developed, which provides a unique access to densely functionalized acyclic ketones bearing β- quaternary carbon centers with a remarkable feature that both α- and β-positions of activated alkene are functionalized.

To develop efficient strategies regarding how to construct a carbon−carbon bond formation becomes a central theme in synthetic organic chemistry due to its unique role in assembling the diverse and complex carbon frameworks. Within this field, the generation of an all-carbon-substituted quaternary center is fundamentally important and represents a great challenge.[1] As one of the most straightforward and atom-economical C−C bond-formation reactions, the transition metal-catalyzed acylcyanation reaction of alkynes and alkenes has received more considerable attention.[2] In particular, a transition metal-catalyzed intramolecular acylcyanation reaction of alkenes has emerged as a powerful tool for preparing functionalized nitriles incorporating an all-carbon-substituted quaternary center, because this atom-economical transformation allows simultaneous installation of both carbonyl and cyano functional groups in a highly selective and efficient manner (Scheme 1, eq 1).[3] However, these intramolecular transformations employed electron-rich alkenes as substrates with limited functional group compatibility and required harsh reaction conditions. In addition, these processes were restricted to the cyanocarbamoylation of alkenes which provide cyclic compounds,[3] while the installations of other acyl groups have not been exploited. With the goal of developing efficient metal-free processes to construct the diverse carbon frameworks incorporating quaternary carbon centers,[4] we are interested in a Lewis base catalyzed acylcyanation of electron-deficient alkenes which may have advantages such as: (i) providing a

(1) For reviews on the construction of a quaternary carbon centers, see: (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (d) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (e) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (f) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (g) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (h) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583. (i) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295. (j) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593.

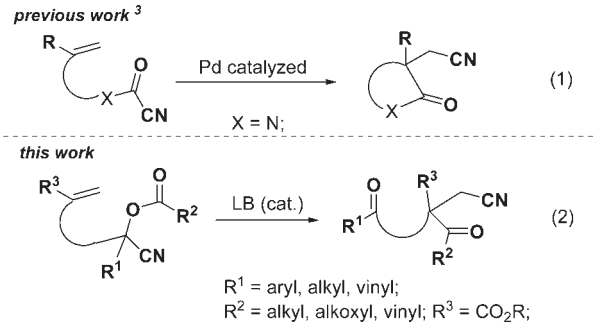
(2) For alkynes as substrates, see: (a) Nozaki, K.; Sato, N.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 2679. (b) Nozaki, K.; Sato, N.; Takaya, H. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1629. (c) Hirata, Y.; Yada, A.; Morita, E.; Nakao, Y.; Hiyama, T.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2010**, *132*, 10070. For alkene as substrates, see: (d) Nishihara, Y.; Inoue, Y.; Itazaki, M.; Takagi, K. *Org. Lett.* **2005**, *7*, 2639. (e) Nishihara, Y.; Inoue, Y.; Izawa, S.; Miyasaka, M.; Tanemura, K.; Nakajima, K.; Takagi, K. *Tetrahedron* **2006**, *62*, 9872. (f) Nakao, Y.; Hirata, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 7420. (g) Hirata, Y.; Inui, T.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 6624.

(3) For intramolecualr acylcyanation of alkenes, see: (a) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303. (b) Najara, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2452. (c) Yasui, Y.; Kamisaki, H.; Ishida, T.; Takemoto, Y. *Tetrahedron* **2010**, *66*, 1980.

(4) (a) Zhuang, Z.; Pan, F.; Fu, J.-G.; Chen, J.-M.; Liao, W.-W. *Org. Lett.* **2011**, *13*, 6164. (b) Pan, F.; Chen, J.-M.; Zhuang, Z.; Fang, Y.-Z.; Zhang, S. X.-A.; Liao, W.-W. *Org. Biomol. Chem.* **2012**, *10*, 2214.

10.1021/ol3007716
Published on Web 04/26/2012

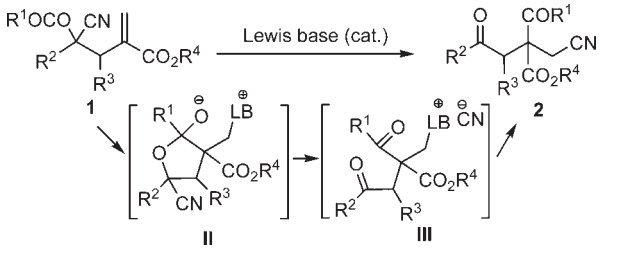
Scheme 1. Intramolecular Acylcyanation of Alkenes Reported and in This Work



metal-free access to highly functionalized nitriles with diverse functional group compatibility in a single step; (ii) from readily available starting materials; and (iii) under neutral and mild conditions. Although Lewis base catalyzed acylcyanation of carbonyl compounds and imines have been studied extensively in recent years,[5,6] an intramolecular acylcyanation reaction of activated alkenes catalyzed by Lewis base has not been developed.

Herein, we report an unprecedented phosphine promoted intramolecular acylcyanation of α-substituted activated alkenes which provides an unique access to densely functionalized acyclic ketones bearing β-quaternary carbon centers with the remarkable feature that both α- and β-positions of activated alkene are functionalized (Scheme 2, eq 2).[7]

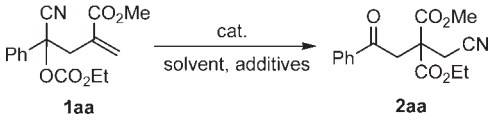
Scheme 2. Proposed Reaction Pathway



Recently, we developed a novel synthetic strategy to furnish the highly functionalized cyanohydrins **1**.[4a] We envisioned that these valuable cyanohydrins **1** with a tertiary alcohol moiety as well as cyanide and allylic functional groups may serve as suitable scaffolds for exploring an unique intramolecular acylcyanation reaction with α-substituted activated alkenes as the substrate. We hypothesized that a possible conjugate addition of Lewis base catalyst to the activated terminal alkene moiety of cyanohydrins **1** and followed by a tandem intramolecular condensation with the ester group and an elimination would afford a phosphonium salt **III** with cyanide ion as a counterion. Subsequently, a S_N2 substitution of intermediate **III** could furnish densely functionalized desired product **2** by utilizing the nucleophilicity of cyanide ion (Scheme 2).[8]

To assess the feasibility of this transformation, an initial investigation was examined with *O*-ethoxycarbonyl protected cyanohydrins **1aa** in acetonitrile with a catalytic amount of PPh_3 (20 mol %), which were readily prepared from the cyanation-allyic-alkylation reaction.[4a] Gratifyingly, this reaction gave rise to highly functionalized ketone **2aa** with a quaternary carbon atom incorporated, whose structure is unambiguously supported by ^1H NMR and ^{13}C NMR spectra, albeit rather sluggishly (Table 1, entry 1). More electron-rich phosphine catalysts were employed and afforded desired product in increased yields (Table 1, entries 2–4). Tertiary amines, such as DMAP, DABCO, and DBU, were also evaluated. However, all of them gave desired product **2aa** in relatively low yields, even at elevated temperature (Table 1, entries 5–7). Solvent optimization showed that this acylcyanation reaction

Table 1. Optimization of Phosphine Promoted Intramolecular Acylcyanation of α-Substituted Activated Alkene **1a**[a]



entry	cat.	solvent	temp (°C)	time (h)	yield (%)[b]
1	PPh_3	CH_3CN	60	36	24
2	PPh_2Et	CH_3CN	30	2	45
3	$PPhEt_2$	CH_3CN	30	0.5	62
4	PBu_3	CH_3CN	30	0.5	53
5	DABCO	CH_3CN	80	24	40
6	DMAP	CH_3CN	80	24	45
7	DBU	CH_3CN	30	1	41
8	$PPhEt_2$	DMF	30	0.5	73
9[c]	$PPhEt_2$	DMF	30	0.5	81
10[c,d]	$PPhEt_2$	DMF	30	0.5	89

[a] Reactions were performed with **1aa** (0.1 mmol) and 20 mol % of catalyst in solvent (c = 0.1 M). [b] Isolated yield. [c] Reaction was carried out in solvent (c = 0.02 M). [d] 4 Å molecular sieve was added.

(5) For examples of Lewis base catalyzed the acylcyanation of carbonyl compounds, see: (a) Poirier, D.; Berthiaume, D.; Boivin, R. P. *Synlett* **1999**, 1423. (b) Berthiaume, D.; Poirier, D. *Tetrahedron* **2000**, *56*, 5995. (c) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195. (d) Baeza, A.; Najera, C.; Retamosa, M. G.; Sansano, J. M. *Synthesis* **2005**, *16*, 2787. (e) Tian, S. K.; Deng, L. *Tetrahedron* **2006**, *62*, 11320. (f) Peng, D.; Zhou, H.; Liu, X.-H.; Wang, L.-W.; Chen, S.-K.; Feng, X.-M. *Synlett* **2007**, 2448. (g) Matsukawa, S.; Sekine, I.; Iitsuka, A. *Molecules* **2009**, *14*, 3353.

(6) For recent examples of Lewis base catalyzed the acylcyanation of imines, see: (a) Pan, S. C.; Zhou, J.; List, B. *Synlett* **2006**, 3275. (b) Pan, S. C.; List, B. *Synlett* **2007**, 318. (c) Pan, S. C.; Zhou, J.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 612. (d) Pan, S. C.; List, B. *Org. Lett.* **2007**, *9*, 1149.

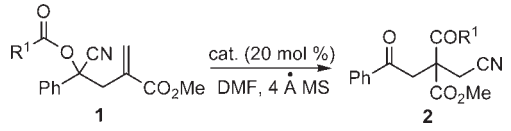
(7) For reviews of nucleophilic phosphine catalysis, see: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (c) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (d) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102. (e) Marinetti, A.; Voituriez, A. *Synlett* **2010**, 174.

(8) Phosphine catalyzed transformations *via* an intramolecular S_N2 substitution to release catalyst, see: Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12928.

proceeded well in DMF in the presence of 20 mol % $PPhEt_2$ or PBu_3.[9] Given the possibility of the intramolecular mechanism of this reaction involved, the reaction of **1aa** was carried out at dilute concentration. Indeed, an increased yield was observed as the reaction was performed in dilute DMF (Table 1, entry 9). The yield of **2aa** could be further enhanced by employing this reaction in dilute DMF in the presence of a molecular sieve (Table 1, entry 9). Finally, optimal reaction condition was obtained when the reaction was conducted in dilute DMF in the presence of 4 Å MS and furnished desired product **2aa** in 89% yield. (Table 1, entry 10).

With optimal reaction conditions in hand, a variety of different *O*-acyl protected cyanohydrins **1** were investigated first. The results are summarized in Table 2.

Table 2. Phosphine-Promoted Intramolecular Acylcyanation of Various *O*-acyl Protected Cyanohydrins[a]



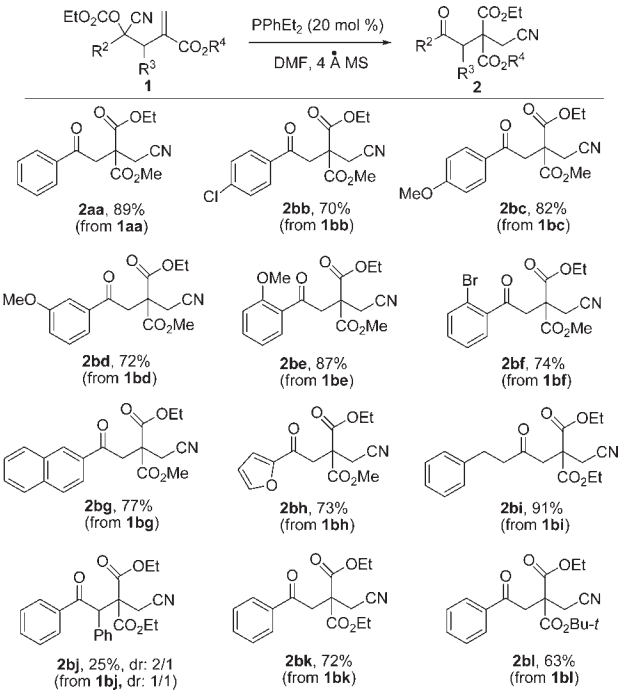
entry	R^1	**1**	temp (°C)	time (h)	yield(%)[b]
1	OEt	**1aa**	30	0.5	89(**2aa**)
2	OBn	**1ab**	30	2	71(**2ab**)
3[c]	Me	**1ac**	60	18	80(**2ac**)
4[c]	Et	**1ad**	30	6	48(**2ad**)
5	Ph	**1ae**	30	–	–[d]
6[c]	(*E*)-PhCH=CH	**1af**	60	36	16(**2af**)
7[c]	$(CH_3)_2C$=CH	**1ag**	60	36	41(**2ag**)
8	H	**1ah**	30	–	–[d]

[a] Reactions were performed with **1** (0.1 mmol), 4 Å molecular sieve, and 20 mol % of $PPhEt_2$ in DMF (c = 0.02 M). [b] Isolated yield. [c] PBu_3(20 mol %) was used. [d] No desired product was detected.

Besides cyanohydrin carbonate **1aa**, *O*-benzyloxycarbonyl protected cyanohydrin carbonate **1ab** also furnished the functionalized ketone **2ab** in high yield (Table 2, entry 2). Cyanohydrin esters other than carbonates were employed and displayed the variant reactivities. *O*-acetyl protected cyanohydrin **1ac**, which may afford 1,4-diketone, gave the desired product **2ac** at a raised temperature in 80% yield in the presence of 20 mol % PBu_3 (Table 2, entry 3). When *O*-acryl protected cyanohydrins **1ad** was employed, the acylcyanation reaction furnished the desired product **2ad** in 48% yield (Table 2, entry 4). However, benzoyl cyanohydrin **1ae** did not provide any desired product under the modified reaction conditions (Table 2, entry 5), presumably due to the steric hindrance effect. Further performing this reaction with cinnamoyl analog **1af** under optimal reaction conditions afforded the desired unsaturated ketone **2af** in low yield (Table 2, entry 6). Considering the possible instability of α, β-unsaturated ketones under selected reaction conditions,[10] *O*-3-methylcrotonoyol protected cyanohydrin **1ag** was employed, and unsaturated ketone **2ag** was obtained in improved yield indeed (Table 2, entry 7). *O*-formyl protected group of cyanohydrin **1ah** seemed to be fragile under optimal reaction conditions, and the reaction failed to give the desired product.

Next, an intramolecular acylcyanation of a spectrum of *O*- ethoxycarbonyl protected cyanohydrins with a variety of substituents located at the α-position of the cyano-group was surveyed to explore the generality of this transformation. The results are summarized in Scheme 3. The reaction proceeded well regardless of whether the aromatic group has an electron-withdrawing (**2bb**) or an

Scheme 3. Phosphine Promoted Intramolecular Acylcyanation of Various Cyanohydrins[a,b]



[a] For full experimental details, see the Supporting Information. [b] Isolated yield.

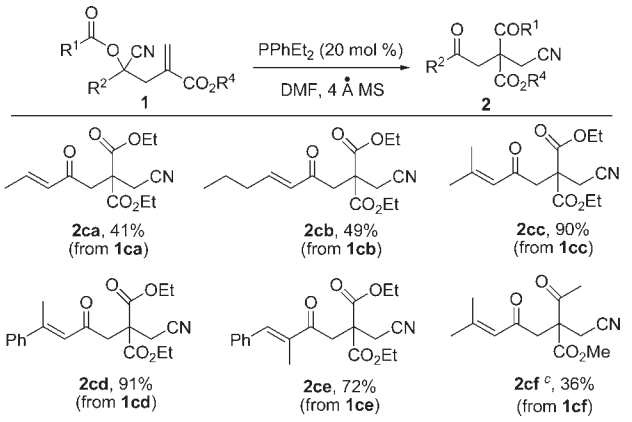
electron-donating (**2bc**) groups and whether the aromatic group is substituted at the para- (**2bb** and **2bc**), meta- (**2bd**), or ortho- (**2be** and **2bf**) position. β-Naphthyl and hetero-aromatic subsititued cyanohydrins can also serve as good substrates and provided desired products in comparably good yields (**2bg** and **2bh**). Cyanohydrin **1bi** with an aliphatic group located at the α-position of cyano-group was next prepared and evaluated. As expected, the reaction afforded ketone **2bi** in excellent yield. Noteworthily, sterically congested cyanohydrin **1bj** was employed and smoothly converted to the desired ketone **2bj** with adjacent

(9) See Supporting Information for details.

(10) The stability of α,β-unsaturated ketone **2ca** was tested. Submitting **2ca** to the optimal reaction conditions in 24 h, **2ca** was recovered in 29% yield along with some unindentified substances.

quaternary and tertiary centers in 25% yield. Furthermore, cyanohydrin carbonates with different ester moieties have been applied in the developed process (**2bk** and **2bl**). The substrate **1bl** with bulkily ester group gave the product **2bl** in relatively low yield.

Scheme 4. Phosphine Promoted Intramolecular Acylcyanation of Various Vinyl (R^2) Cyanohydrins[a]



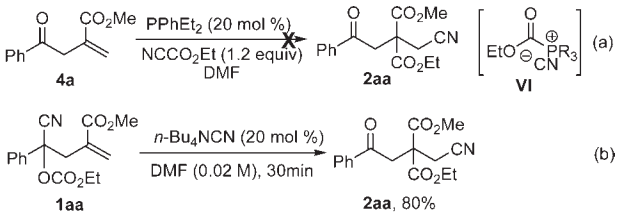
[a] For full experimental details, see the Supporting Information.
[b] Isolated yield.
[c] PBu_3 (20 mol %) was used.

In the course of further studies, cyanohydrin carbonates **1** with vinyl substituents located at the α-position of the cyano group were evaluated (Scheme 4). In contrast with phosphine promoted intramolecular acylcyanation of *O*-α,β-unsaturated acyl protected cyanohydrin (**1af** and **1ag**), cyanohydrins **1** with vinyl substituents located at the α-position of the cyano group add a new dimension to the scope of these reactions. The linear vinyl substituted cyanohydrins (**1ca** and **1cb**) afforded unsaturated ketones **2ca** and **2cb** in relatively low yields (**2ca** and **2cb**). Thus, the branched vinyl substituted cyanohydrin carbonate **1cc** was investigated. To our delight, this process furnished the desired unsaturated ketone **2cc** in high yield with high efficiency. Other branched vinyl substituted cyanohydrin carbonates also provided good to excellent results under the optimal reaction conditions (**2cd** and **2ce**). In addition, intramolecular acylcyanation of cyanohydrin acetate **1cf** has been investigated and gave rise to unsaturated 1,4-diketone **2cf** in 36% yield.

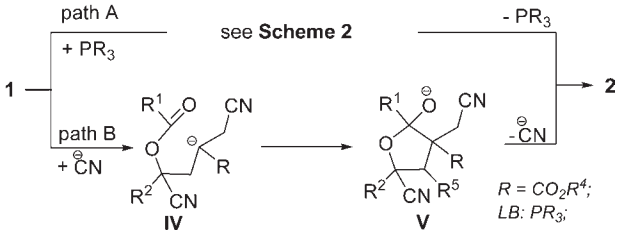
To gain some preliminary mechanistic understanding of this intramolecular transformation, control experiments were conducted (Scheme 5). Since phosphines can undergo 1,2-addition to carbonyl compounds,[7b,5g] a possible alternative mechanism is that the attack of phosphine at the C=O bond of *O*-acyl group of cyanohydrin **1aa**, which results in ketone **4a** and acylphosphonium salt (**VI**), and

(11) Recent examples for conjugate addition of cyanide to α,β-unsaturated carbonyl compounds, see: Tanaka, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 8862; see Supporting Information for further references..

Scheme 5. Control Experiments and Mechanistic Proposal



mechanistic proposal:



followed by an insertion of **VI** across the C=C bond of **4a** could lead to a final product. However, this possibility was ruled out due to the fact that treatment of ketone **4a**, ethyl cyanoformate, and $PPhEt_2$ (20 mol %) did not provide the desired product (Scheme 5a). Interestingly, the treatment of substrate **1aa** with tetrabutylammonium cyanide (20 mol %) provided **2aa** in 80% yield as well, which indicated that cyanide ion can promote this process alone (Scheme 5b).[11] Based on these investigations, it is also possible that cyanide ion generated in situ could undertake a tandem transformation to provide the desired product (Scheme 5, path B). Further studies of the reaction mechanism are ongoing in our laboratories and will be reported in due course.

In summary, we have developed a novel phosphine promoted intramolecular acylcyanation reaction of α-substituted activated alkenes, which are prepared from readily available starting materials. This protocol provides a facile access to construct quaternary carbon centers under neutral and mild conditions. The broad scope and versatility of the process was demonstrated by the introduction of a variety of alkyl, aryl, allylic, and heteroaryl substituents at multiple sites in the densely functionalized ketone products.

Acknowledgment. This work is supported by NSFC (no. 21102054) and Open Project of State Key Laboratory for Supramolecular Structure and Materials (sklssm201220). Special gratitude goes to Professor Sean Xiao-An Zhang (College of Chemistry, Jilin University, China) for his long-term support.

Supporting Information Available. General procedure and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org. The authors declare no competing financial interest.

The authors declare no competing financial interest.