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Theoretical study on the mechanism of *N*-heterocyclic carbene catalyzed transesterification reactions

Chun-Liang Lai, Hon Man Lee and Ching-Han Hu*

Department of Chemistry, National Changhua University of Education, Changhua 50058, Taiwan

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Abstract—The mechanism of *N*-heterocyclic carbene (NHC) catalyzed transesterification reactions have been studied using density functional theory. Our study shows that the role of NHC is to assist proton transfer from alcohol to the carbonyl oxygen, forming the tetrahedral intermediate, which then decomposes to the acylated product. Our predicted activation energies are in fine agreement with the observed reaction rates. An alternative approach, which uses the tetrahedral intermediate as the transition state mimic, provides satisfactory predictions.

1. Introduction

Since the breakthrough isolation of *N*-heterocyclic carbene (NHC) by Arduengo et al., preparations of NHC has become accessible to chemists.[1,2] NHCs are basic, soft, and nucleophilic species; they are also recognized as good σ-donors and poor π-acceptors.[3–5] Due to their extraordinary properties, NHCs were found to be involved in a variety of catalytic processes.[3,6,7] Studies for the applications of NHC ligands in organometallic chemistry have intensified in the past few years. The new generation of NHC catalysts have supplemented the role of traditional phosphine catalysts. Moreover, the phosphine ligands are in part replaced by NHCs due to the demonstrated excellence in homogeneous catalysis of the latter.[8] One of the most well established applications of NHC is the second-generation Grubbs' ruthenium–NHC complexes, which catalyze olefin-metathesis reactions.[7,8] NHC has also been demonstrated to be excellent ligands in complexes, which catalyze Heck and Suzuki coupling reactions.[9–11]

In addition to the aforementioned developments in organometallic applications, there is a growing use of NHCs in organocatalysis.[12] The potential applications of NHC in this area is demonstrated by the successes in nucleophilic aromatic substitutions, direct annulations of enals and aldehydes, and in the enantioselective acylation of racemic alcohols.[13–17]

Very recently, NHC has been shown by Nolan and Hedrick's research groups to perform transesterification reactions with great success.[18–23] These NHCs are imidazol-2-ylidenes and imidazolin-2-ylidenes, and some typical examples are shown in Scheme 1. An impressive example given by Nolan and co-workers is the reaction of benzyl alcohol with vinyl acetate (in THF), in which the ester is almost quantitatively converted to benzyl acetate in 5 min with NHC catalyst.[18] In addition, Hedrick and co-workers have demonstrated that NHC acts as catalyst for the living ring-opening polymerization of cyclic esters.[21,22] In these NHC catalyzed reactions, improved selectivity between the primary and secondary alcohols was observed.[20] The acylation of primary alcohols dominates with the presence of secondary alcohols.[18] The widely available methyl or ethyl esters are usually inert to transesterifications, however, they can be catalyzed by NHC along with the use of molecular sieves.[18]

Ester is an ubiquitous type of compound in chemistry. Transesterification, which takes place via an alkoxy moiety exchange between ester and alcohol, is a mild and versatile alternative to esterification using acid and alcohol, which suffers from harsh reaction conditions.[20] NHC has proven to be both efficient and selective in transesterification reactions. In this study, we present our research on the mechanism of NHC catalyzed

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Keywords: Transesterification; Density functional theory; NHC.

* Corresponding author. Tel.: +886 47232740; fax: +886 47211190; e-mail: chingkth@cc.ncue.edu.tw

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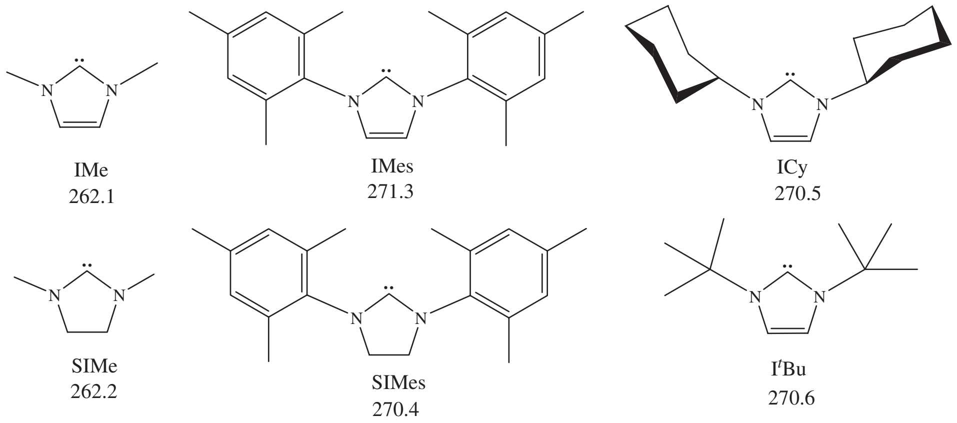


Scheme 1. NHCs and their gas phase proton affinity (in kcal/mol).

transesterification. We will also demonstrate that the tetrahedral intermediate serves as a transition state (TS) analogue, and this feature promises computationally economic theoretical predictions.

The theoretical treatment of the systems included in this work were performed by the B3LYP density functional approach using the Gaussian03 series of programs.[24] The approach is a hybrid method, which includes Becke's three-parameter mixing of gradient-corrected exchange potential[25] and the correlation functional of Lee, Yang, and Parr.[26] We used Dunning's correlation-consistent cc-pVDZ basis set in the calculations.[27] Harmonic vibrational frequencies were used to verify the genuine minima and transition states on the potential energy surface (PES). Zero-point vibrational energies were included in internal energies (E_0) and Gibbs free energies (G). At the located transition structures, we performed the intrinsic reaction coordinate (IRC) computation[28] to ascertain whether it connects the reactant and product.

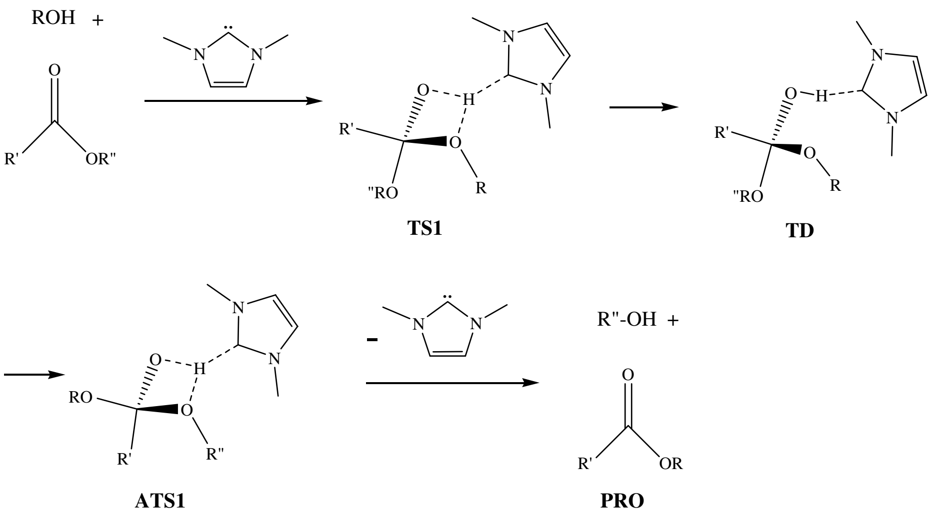
For the discussions concerning reaction mechanism involving ionic species, we investigated the related species using the polarized continuum model (CPCM) of Barone and Cossi to include the solvation effects.[29] The CPCM optimized geometries of species on PES were obtained both for the neutral and ionic reaction paths, followed by a single point computation using a larger basis set, aug-cc-pVTZ.

Two mechanisms were considered in our study, the first reaction involves a neutral tetrahedral intermediate, while the second reaction involves an ionic tetrahedral intermediate.

2. Mechanism involving a neutral tetrahedral intermediate

This mechanism consists of two stages, which begins with the formation of tetrahedral intermediate (**TD**) followed by the dissociation of tetrahedral intermediate to form product ester (Scheme 2).

We have examined the PES of the reactions between methyl acetate and alcohols including MeOH, EtOH, ^{i}PrOH, and ^{t}BuOH. We chose 1,3-dimethylimidazol-2-ylidene (IMe) as the catalyzing NHC. The computed



Scheme 2. Proposed mechanism for NHC catalyzed transesterification involving a neutral tetrahedral intermediate.

Table 1. Relative energies (in kcal/mol) of the stationary points involved in the NHC catalyzed transesterification reaction. Reactions are catalyzed by IMe, with methyl acetate being the ester

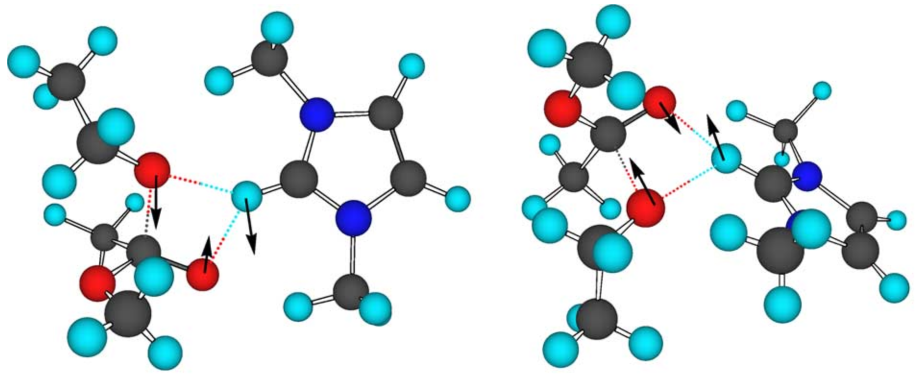
	Alcohol	**TS2**	**OHI**	**TS1**	**TD**	**ATS1**	**PRO**
ΔG	MeOH	24.1	−0.4	27.0	16.0	27.0	0.0
	EtOH	23.6	0.2	27.9	16.8	28.0	0.4
	^{i}PrOH	23.3	2.6	30.0	19.04	29.4	1.5
	^{t}BuOH	24.8	8.8	37.1	23.4	33.6	5.0
	MeOH[a]	21.7	−10.4	28.7	16.2	28.7	0.0
ΔE_0	MeOH	13.5	−12.3	3.1	−6.7	3.1	0.0
	EtOH	12.9	−11.9	3.8	−6.4	3.6	0.3
	^{i}PrOH	12.9	−9.8	5.4	−4.7	4.9	1.1
	^{t}BuOH	13.7	−4.1	11.5	−1.2	8.8	4.1
	MeOH[a]	10.5	−22.7	4.3	−6.7	4.3	0.0

[a] Reaction catalyzed by 1,3-dimethylimidazolin-2-ylidene (SIMe).

relative energies (ΔE_0) and Gibbs free energies (ΔG) at 298 K are summarized in Table 1. For the reactions of EtOH, ^{i}PrOH, and ^{t}BuOH the transition states and tetrahedral intermediates are enantiomeric. Our computation shows that in all three cases the transition states and tetrahedral intermediates of the *S*-enantiomers are slightly lower in energy than their *R*-counterparts (see Supporting data). The structures of **TS1** and **TD** for the reaction involving EtOH are illustrated in Figure 1.

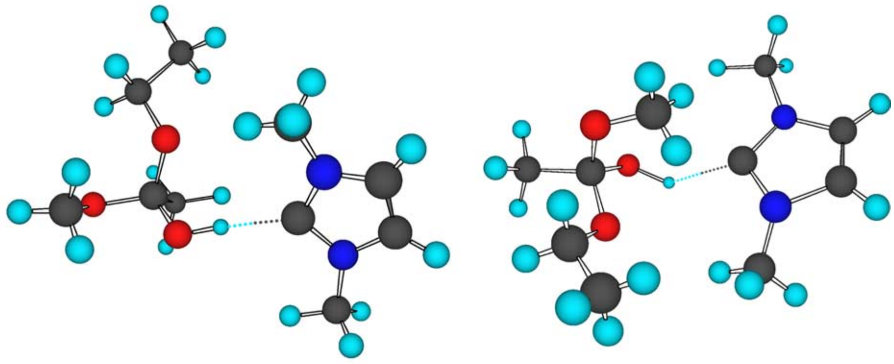
PES for the reaction involving MeOH is symmetric, thus **TS1** and **ATS1** are identical. For the other alcohols, the relative energies of the second transition state (**ATS1**) are slightly smaller. The largest difference is observed for ^{t}BuOH, for which **ATS1** is 3.5 kcal/mol lower than **TS1**. The ΔE_0 of **TS1** are 3.1, 3.8, 5.4, and 11.5 kcal/mol for MeOH, EtOH, ^{i}PrOH, and ^{t}BuOH, respectively. The corresponding ΔG values of **TS1** are 27.0, 27.9, 30.0, and 37.1 kcal/mol. The result in Table 1 clearly shows that the reaction barrier for primary alcohol is the lowest. Secondary alcohol (^{i}PrOH) has a slightly higher barrier, while for the tertiary alcohol (^{t}BuOH), the reaction barrier is noticeably increased. Thermodynamically, it is also seen that the free energy of reaction for ^{t}BuOH (5.0 kcal/mol) is noticeably the largest, and that of ^{i}PrOH (1.5 kcal/mol) is larger than that for EtOH (0.4 kcal/mol) and MeOH. Using IMe and IMes, it has been shown by Hedrick's group that at equilibrium the conversion ratio of ^{i}PrOH is slightly lower than that of EtOH (with methylbenzoate); in contrast, the conversion of ^{t}BuOH is negligible.[21] Nolan's group has also demonstrated marked selectivity in kinetically controlled transesterifications of benzyl alcohol and 2-butanol in the presence of IMes (with vinyl acetate).[19]

The geometrical parameters (see Supplementary data) of the TSs reveal how NHC catalyzes the transesterification



S-**TS1**
i 95 cm^{-1}
ΔG= 27.9

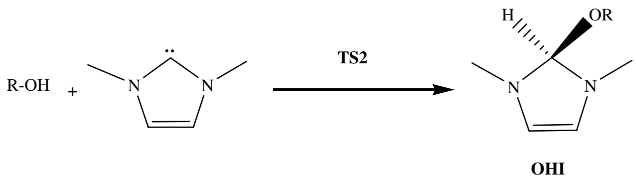
R-**TS1**
i 161 cm^{-1}
ΔG= 28.3



S-**TD**
ΔG= 16.8

R-**TD**
ΔG= 17.3

Figure 1. B3LYP/cc-pVDZ structures and relative energies (in kcal/mol) for the *R*- and *S*-enantiomers of **TS1** and **TD**. The reactants are EtOH and methyl acetate, catalyzed by IMe. Refer to Supplementary data for more data.



Scheme 3.

reaction. The normal motion associated with the imaginary frequency of TS is characterized as proton transfer from the alcohol to the carbonyl oxygen, leading to the tetrahedral intermediate. It would be interesting to compare NHCs with the amine catalyzed reactions. The ΔG values of **TS1** in the reactions of methylacetate and EtOH catalyzed by trimethylamine, pyridine, and imidazole are as high as 45.9, 49.7, and 50.9 kcal/mol, respectively.

An O–H insertion product (**OHI**) and the transition state leading to it (**TS2**) have been located on the PES (Scheme 3). An alternative reaction could occur through **OHI**, and form **TD** via **TS1**. To verify this possibility, we performed the IRC calculation from **TS1**. The only **TS1** that leads to **OHI** is that of ^{t}BuOH, in which IRC calculations of the other alcohols lead to the reactants. Since **TS1** is the rate limiting transition state, this branch reaction will not concern our later discussions.

3. Imidazolin-2-ylidene versus imidazol-2-ylidene

Although less often used in NHC catalyzed reactions, it would be insightful to compare the catalytic capacity of imdazolin-2-ylidene, the 4,5-saturated counterpart of imidazol-2-ylidene. The results of 1,3-dimethylimidazolin-2-ylidene (SIMe) catalyzed reaction (methyl acetate and methanol) in Table 1 shows that the free energy of activation at **TS1** for SIMe is 1.7 kcal/mol higher than that of IMe. ΔG for the **TD** catalyzed by SIMe is also slightly higher in energy than that of IMe. The difference in the activation barrier indicates that the catalytic capacity of imidazol-2-ylidene is better. As has been demonstrated in the reaction of methyl acetate and benzyl alcohol, the conversion rate is higher with IMes than with SIMes.[19]

4. Mechanism involving an anionic tetrahedral intermediate

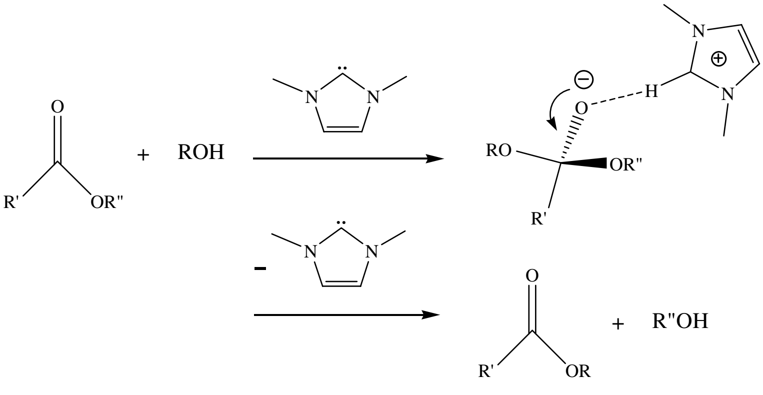
An alternative mechanism involves the formation of alkoxide by proton abstraction by NHC from the alcohol, followed by nucleophilic attack of the alkoxide anion to the carbonyl carbon. The mechanism involves an ionic tetrahedral intermediate as illustrated in Scheme 4. We investigated this mechanism using the B3LYP/cc-pVDZ theory, and included the solvation effects with the CPCM model. The dielectric constant of THF ($\varepsilon = 7.58$) is used in our computation, in which the CPCM optimized geometries are obtained. A single point computation using aug-cc-pVTZ basis set was followed to obtain solvation free energy. With THF, the zwitterionic tetrahedral intermediate is 3.1 kcal/mol higher in free energy than the neutral one (**TD**). At the MP2/cc-pVDZ level of theory, the energy difference is 2.2 kcal/mol. In addition, the tetrahedral anion and the imidazolium cation are 9.1 kcal/mol higher in free energy than those of the neutral tetrahedral intermediate plus NHC. Our results suggest that the mechanism involving proton abstraction and nucleophilic attack of alkoxide anion, is not favored energetically.

5. Mechanism involving nucleophilic acylation of NHC

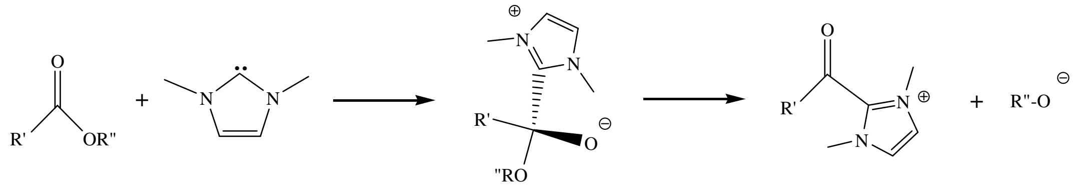
Another possible mechanism involves the nucleophilic attack of NHC to the carbonyl carbon, resulting either in the tetrahedral zwitterionic intermediate[18–23] or 2-acylimidazolium intermediate[16] (Scheme 5). With the inclusion of solvation effects, these two intermediates are 22.5 and 60.0 kcal/mol higher in free energy than the starting molecules, respectively. Comparing with **TD** of the same system (16.0 kcal/mol), this mechanism is less likely to occur.

6. Tetrahedral intermediate as transition state analogue

In Table 1, we see that the relative energies of the tetrahedral intermediates are proportional to those of the transition states leading to them, and are also proportional to the reaction energies. Thus, the tetrahedral



Scheme 4. Mechanism for NHC catalyzed transesterification involving an ionic tetrahedral intermediate.



Scheme 5.

intermediate may serve as 'transition state analogue' for the transesterification reaction. Since for larger sized substrate and NHC, a full optimization of the stationary points involved in the reaction path can be a formidable task. Exploration for the possibility of applying a transition state analogue, that is the tetrahedral intermediate, is intriguing. For this purpose, we examined several reactions, from which we can compare our results with the experimental rates.

The relative energies (ΔE) of **TD** of the reactions catalyzed by different NHCs are summarized in Table 2. We have computed these energies using B3LYP and the much more computationally economic semi-empirical method, PM3.[30] At the PM3 level we have verified that the *S*-enantiomers of **TD** are lower in energy than their *R*-counterparts. For the reaction of methyl benzoate with alcohols, we can see that for both IMe and IMes the relative energies of **TD** are in the order primary < secondary < tertiary alcohol. The ΔE for tertiary alcohols are significantly higher than those for the primary and secondary alcohols. It is noted that, PM3 method provides comparable predictions to DFT. B3LYP shows that the ΔE of rthe eactions catalyzed by IMe are lower than those of IMes. This difference is more likely attributed to steric repulsions rather than electronic effect, since the gas phase proton affinity of IMes is 9.2 kcal/mol larger than that of IMe (Scheme 1). However, PM3 prediction shows the opposite for the relative barriers of IMe versus IMes. PM3 is more reliable in predicting relative activation energies between various alcohols.

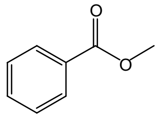
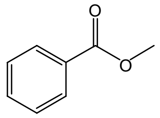
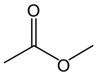
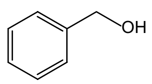
For the reaction between methyl acetate and benzyl alcohol, we computed the relative energies of the tetrahedral intermediates catalyzed by six NHCs. We see that the lowest relative energy occurs with ICy. The less bulky carbenes IMe and SIMe have lower ΔE than IMes and SIMes. We have also noticed that the activation barriers of the 4,5-unsaturated NHCs are lower than their 4,5-saturated counterparts, that is, IMe < SIMe and IMes < SIMes. This trend is seen both in B3LYP and PM3 predictions. In general, the predicted ΔE are in good accord with the experimental observations made by Nolan's group,[20] which concluded that ICy is a better catalyst than IMes, and IMes is a better catalyst than SIMes.

The only odd result from the TD approach occurs in the case of I^{t}Bu, in which the B3LYP predicted that ΔE is highest among all the NHCs, while according to the experiment of Nolan et al. its catalytic capacity is comparable to ICy. In contrast, the PM3 energy shows that the ΔE of I^{t}Bu is close to that of ICy.

Overall, our exploration on using the tetrahedral intermediate as the transition state analogue has provided quite successful predictions. This is encouraging for future studies in transesterification reaction involving larger molecules.

In summary, we have proposed a mechanism for the NHC catalyzed transesterification. The mechanism shows that the role of NHC in catalysis is to assist proton transfer from the alcohol to the carbonyl oxygen to

Table 2. Relative energies (ΔE in kcal/mol) of the tetrahedral intermediates (**TD**) involved in the NHC catalyzed transesterification reactions

Catalyst	Ester	Alcohol	B3LYP/cc-pVDZ	PM3	Conv. %
IMe		EtOH	−5.5	−12.01	79[a]
		^{i}PrOH	−4.6	−9.73	72[a]
		^{t}BuOH	0.0	−2.97	<1[a]
IMes		EtOH	−4.0	−12.23	85[a]
		^{i}PrOH	−2.8	−11.29	11[a]
		^{t}BuOH	2.3	−3.82	<1[a]
ICy			−7.7	−12.9	100[b]
IMe			−7.7	−10.0	
SIMe			−7.0	−9.1	
IMes			−6.5	−10.5	93[b]
SIMes			−6.0	−9.1	21[b]
I^{t}Bu			−5.9	−11.7	100[b]

[a] Conversion rates were measured at equilibrium (20 h of reaction).[21]

[b] 4 Å molecular sieves were used by Nolan and co-workers to absorb methanol.[20]

form a tetrahedral intermediate, the intermediate then decomposes to form acylated product. Very recently, a similar mechanism has been proposed by Movassaghi and Schmidt.[31] Our predicted PESs show that the conversion rate of transesterification is in the order of primary alcohol > secondary alcohol > tertiary alcohols, both kinetically and thermodynamically. NHC with less bulky N-substitutions are more catalytic than the bulkier ones; and 4,5-unsaturated NHCs are more catalytic than their 4,5-saturated counterparts. We have shown that the tetrahedral intermediate is a good approximation to the transition state. This feature allows predictions for the rates of NHC catalyzed transesterification reactions using simpler computations.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.046.

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