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One-Pot Tandem Catalysis: A Concise Route to Fused Bicyclic Scaffolds from Acyclic β-Ketoesters and Alkynyl Aldehydes

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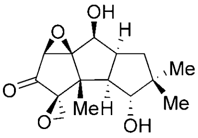
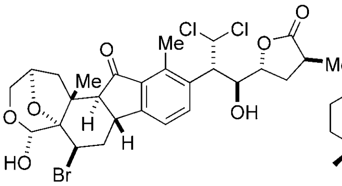
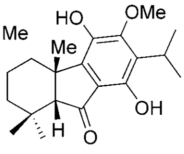
The fused bicyclic skeleton is an important subunit in many natural products, pharmaceuticals, and organic building blocks in organic synthesis (some examples are depicted here).[1] Thus, it is not surprising that various new synthetic methods have been developed for their construction.[2] Within this context, the Conia-ene reaction[3,4] of an alkyne with an enolizable carbonyl group is a fundamental method for carbon–carbon bond formation and is widely used in carbocyclization reactions. For example, Nakamura[4a–c] and Toste[4g–i] have explored metal-catalyzed intramolecular Conia-ene-type reactions, providing a rapid route to a diverse range of carbocycles and heterocycles. The Nazarov cyclization[5,6] is another very versatile method for the synthesis of five-membered carbocycles due to the stereospecific nature of the cyclization. Recently, mechanistic insights into this reaction and its synthetic applications in total synthesis have been well demonstrated by Trauner[6h–j] and Eisenberg and Frontier[6a–g]. In addition, domino reactions and 'one-pot' tandem catalyses[7] have shown their unrivalled power in organic synthesis due to their ability to merge several reactions into one operation. Herein, we report an efficient $In(OTf)_3$-catalyzed (OTf = trifluoromethanesulfonate), highly regio- and diastereoselective tandem reaction, featuring Nazarov-cyclization/Conia-ene-type reactions, that synthesizes fused bicyclic scaffolds from alkynyl dienones (Scheme 1). Furthermore, a concise one-pot strategy was successfully accomplished by combining these tandem reactions with a Knoevenagel condensation, which provides rapid and efficient access to fused bicyclic compounds from readily available β-ketoesters (**1**) and alkynyl aldehydes (**2**; Scheme 1). In this one-pot reaction, piperidinium acetate



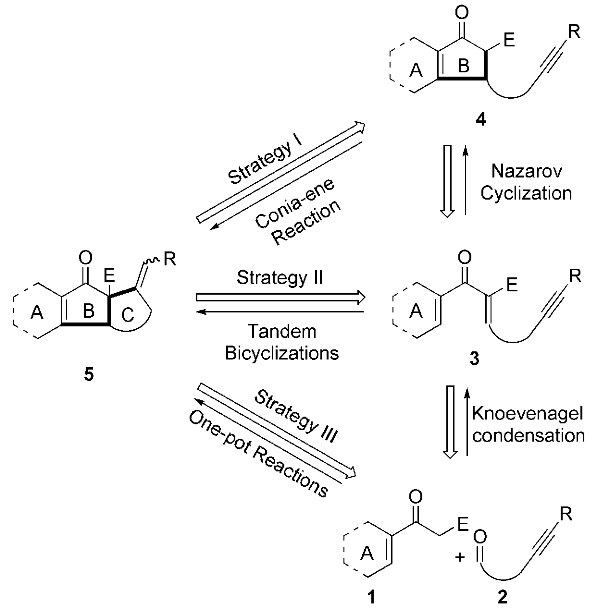
coriolin



Nakiterpiosin



taiwaniaquinol B



Scheme 1. Our proposed strategies for the construction of fused polycyclic scaffold **5**.

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was found to be a novel tandem catalyst that plays important roles in not only the Knoevenagel condensation but also the subsequent tandem reactions.

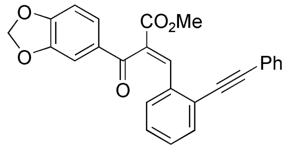
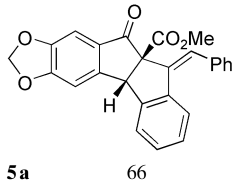
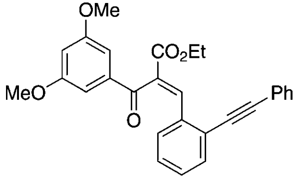
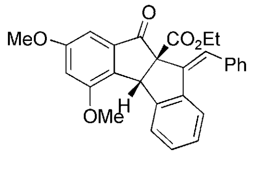
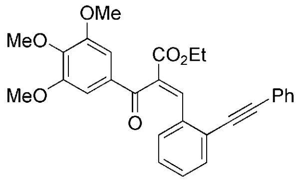
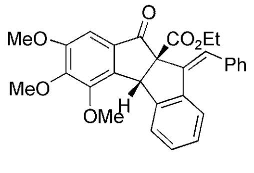
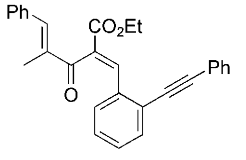
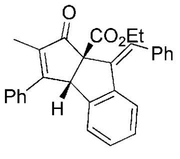
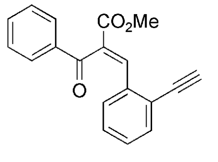
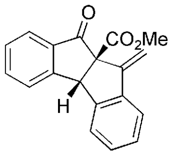
In our efforts to develop tandem reactions,[8] we became interested in the synthesis of the fused polycyclic scaffold **5**. After retrosynthetic analysis of scaffold **5** (Scheme 1), three possible strategies were proposed for its synthesis from readily available β-ketoesters (**1**) and alkynyl aldehydes (**2**). Strategy I is stepwise through the successive construction of rings B and C; Strategy II involves a tandem reaction consisting of a Nazarov cyclization and a Conia-ene-type reaction from precursor **3**, which can be easily prepared by a Knoevenagel condensation of a β-ketoester and an alkynyl aldehyde; the final, 'one-pot' strategy (Strategy III) is the most concise and effective and merges the three different reactions. Evidently, the tandem bicyclization is the key to both strategies II and III. Therefore, we began our study by examining the tandem reactions of **3a** under various conditions.

After numerous attempts, In(OTf)$_3$ (10 mol %) was found to be an effective catalyst for both the Nazarov cyclization and the subsequent 5-*exo-dig* Conia-ene reaction, affording **5a** in 66 % yield, at 80 °C, in toluene (Table 1, entry 1, conditions A). If 1,8-diazabicycloundec-7-ene (DBU; 5 mol %; conditions B) was added the yield could be improved slightly to 70 %, despite the longer time required by the reaction, indicating that the DBU may help the intramolecular Conia-ene reaction by improving the nucleophilicity of the generated enol (Table 1, entry 2; for more details, please see SI-Table 1 in the Supporting Information). Substrates **3b–e**, containing a range of vinyl nucleophiles, were examined under the optimal reaction conditions (Table 1). All of the reactions were highly selective, forming the desired products **5b–d** as single diastereoisomers with a *cis* configuration of the two newly formed five-membered rings and an *E* configuration[4f] of the *exo* double bond. The *endo* product was not detected in the NMR spectrum of the crude product. It was found that the benzo[*d*]-1,3-dioxol-5-yl moiety in **3a** could be replaced by both aromatic rings and substituted alkenes (Table 1, entries 3–5). To our delight, substrate **3e**, with a phenyl group as the vinyl nucleophile, gave the corresponding product **5e** in 81 % yield (Table 1, entry 6).

Next, we examined the effects of the alkyne moiety and the linking chain on the reaction (Table 2). Most of the tandem reactions proceeded smoothly to give the corresponding polycyclic compounds **5** with *cis* configuration and *exo* selectivity. The stereochemistry of the *exo* double bond was *E* except in **5f**, **g**, and **l**. Reactions of **3i**, containing a trimethylsilyl (TMS) group, and **3j** gave the same product **5j**, indicating that the TMS group was not compatible with the reaction conditions (Table 2, entries 4 and 5). The introduction of two electron-donating MeO groups into the linked phenyl ring (**3k**) led to a higher yield, which may result from the easier Nazarov cyclization (comparison of **3a** and **k**).[6b,f] Delightfully, the linked phenyl ring can be replaced by an alkane or an alkene to give the corresponding products in moderate yields (Table 2, entries 7–10). In some cases (Table 2, entries 8 and 10), the *exo* double bond undergoes isomerization under the reaction conditions.[9,10] Furthermore, substrates with longer linking chains were also examined. For example, substrate **3p**, with a three-atom chain, produces compound **5p**, containing a six-membered carbocyclic ring, in 75 % isolated yield (Table 2, entry 11). A seven-membered heterocyclic ring can also be formed (Table 2, entry 12). In contrast, a simple Nazarov cyclization product **4r** (65 % yield) along with decarboxylation product **4r′** (15 % yield) were obtained in the attempts to construct an eight-membered heterocyclic ring (Table 2, entry 13).[11]

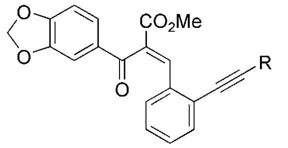
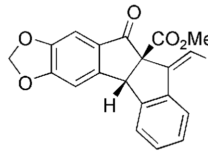
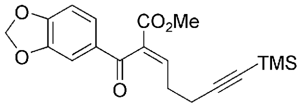
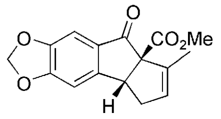
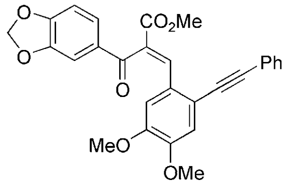
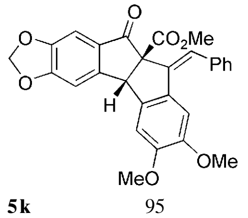
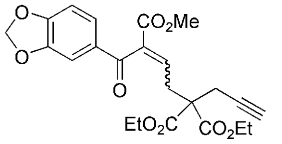
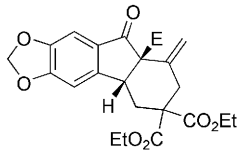
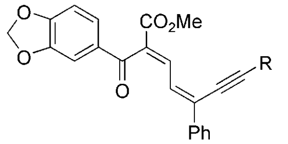
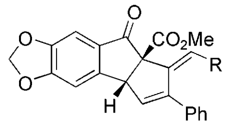
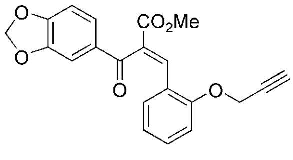
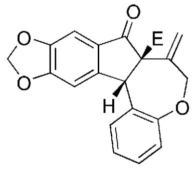
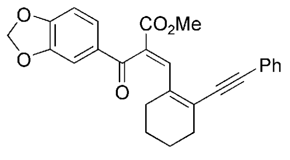
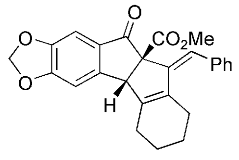
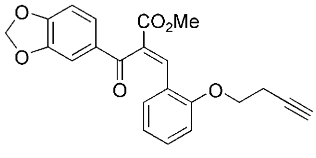
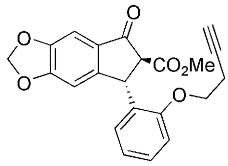
After realizing strategy II, we were eager to examine the 'one-pot' synthetic strategy III, which uses β-ketoesters **1** and alkynyl aldehydes **2** as the starting materials. To our delight, this 'one-pot' strategy was successfully accomplished by the employment of piperidinium acetate (10 mol %) as the catalyst with 4 Å molecular sieves (MS) as an additive

Table 1. Study into the scope of the tandem reactions through variation of the vinyl nucleophile.

Entry	Substrate	Conditions[a]	Product	Yield [%][b]
1	 **3a**	A, 80 °C, 3 h	 **5a**	66
2	**3a**	B, 80 °C, 7 h	**5a**	70
3	 **3b**	B, 60 °C, 24 h	 **5b**	89
4	 **3c**	B, 70 °C, 24 h	 **5c**	71
5	 **3d**	B, 60 °C, 12 h	 **5d**	65
6	 **3e**	B, 110 °C, 11 h	 **5e**	81

[a] Conditions A: substrate (0.1 M) in toluene (3 mL) and In(OTf)$_3$ (10 mol %); conditions B: substrate (0.1 M) in toluene (3 mL), In(OTf)$_3$ (10 mol %), and DBU (5 mol %). [b] Yield of isolated product.

Table 2. Study into the scope of the tandem reaction through variation of the terminal substituent and linking chain.

Entry	Substrate	Conditions[a]	Product	Yield [%][b]	Entry	Substrate	Conditions[a]	Product	Yield [%][b]
									
1	**3f** R=*n*Bu	A, 100°C, 2 h	**5f** R=*n*Bu	70 (22)[c]	10	**3o**	A, 100°C, 2 h	**5o′**	61
2	**3g** R=cHex	B, 80°C, 3 h	**5g** R=cHex	53 (27)[c]					
3	**3h** R=cPr	B, 80°C, 12 h	**5h** R=cPr	80					
4	**3i** R=TMS	A, 100°C, 1 h	**5j** R=H	81					
5	**3j** R=H	B, 80°C, 1 h	**5j** R=H	86					
									
6	**3k**	B, 80°C, 1 h	**5k**	95	11	**3p** (3:2)[e]	A, 110°C, 3 h	**5p** E=CO_2Me	75
									
7	**3l** R=Ph	B, 80°C/24 h	**5l** R=Ph	25 (24)[c]	12	**3q**	A, 110°C, 1 h	**5q** E=CO_2Me	61
8	**3m** R=*n*Bu	A, 70°C, 3 h	**5m** R=*n*Bu	42[d]					
									
9	**3n**	A, 80°C, 6 h	**5n**	70	13	**3r**	A, 80°C, 6 h	**4r**	65[f]

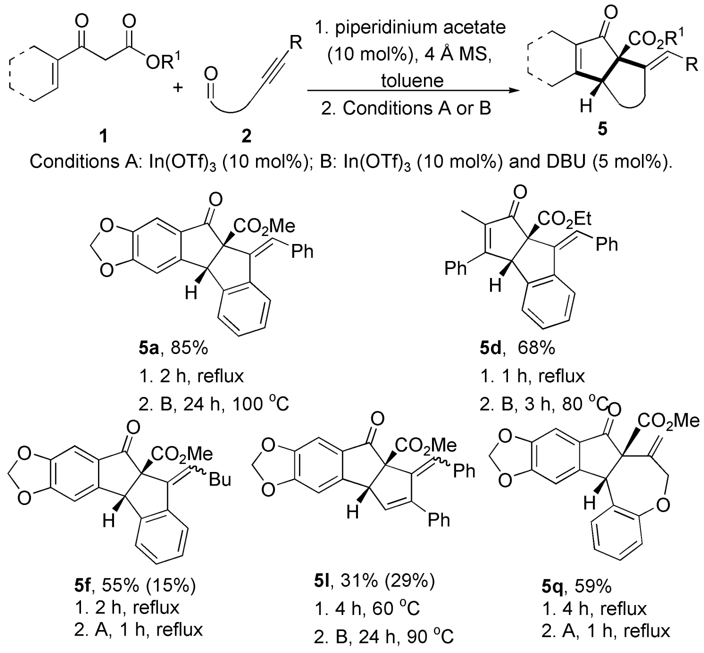
[a] Conditions A: substrate (0.1 M) in toluene (3 mL), In(OTf)$_3$ (10 mol%); conditions B: substrate (0.1 M) in toluene, In(OTf)$_3$ (10 mol%), and DBU (5 mol%); cHex=1-cyclohexenyl; cPr=cyclopropyl. [b] Isolated yield. [c] Isolated yield of *Z* isomer. [d] see ref. [9]. [e] Ratio of *E*,*Z* isomer. [f] see ref. [11].

in toluene and the final products were isolated in 59–85% yields by adding a catalytic amount of In(OTf)$_3$, with or without DBU, after the first condensation step had occurred (Scheme 2). Unexpectedly, the yields of this 'one-pot' strategy were higher than those of strategy II and the by-product of the whole process is H_2O, indicating that this process is highly efficient and environmentally benign.[12]

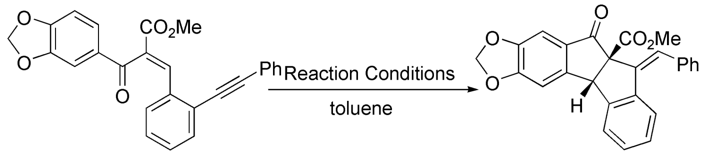
Control experiments (Scheme 3) showed that piperidinium acetate is a novel tandem catalyst,[7d–e] which may promote not only the condensation step but also the Nazarov cyclization/intramolecular Conia-ene-type reactions that follow. The reaction of **3a** under conditions A and piperidinium acetate (10 mol%) gave product **5a** in 74% yield, while 83% yield was obtained under conditions B with piperidinium acetate (10 mol%). Both of these yields are higher than if the piperidinium acetate was absent (66–70%, Table 1, entries 1 and 2).

To gain insight into the role of piperidinium acetate in this tandem reaction, a series of parallel experiments were carried out using substrate **3q**. From [Eq. 1], the addition of piperidinium slows down the transformation of **3q**, but is beneficial to the formation of **5q**. We then used **4q** as the substrate to study the Conia-ene reaction, see [Eq. 2]. After 6.5 h, **4q** was consumed completely and gave **5q** in 95% yield under conditions C [In(OTf)$_3$ (10 mol%) and piperidinium acetate (10 mol%)], whereas **5q** was only formed in 5% yield under conditions A [In(OTf)$_3$ (10 mol%)]. This indicates that the piperidinium acetate accelerates the Conia-ene reaction, but may slightly hinder the Nazarov cyclization.

In summary, we have developed an In(OTf)$_3$-catalyzed, highly diastereoselective tandem Nazarov cyclization/intramolecular Conia-ene-type reaction of alkynyl dienone **3** to synthesize fused polycyclic scaffolds with a quaternary carbon stereocenter. It should be noted that the reactions displayed *exo* selectivity and the fused cyclic systems were formed in *cis* configurations. Furthermore, a one-pot strategy from β-ketoesters **1** and alkynyl aldehydes **2** has been accomplished and is the best strategy,[12] providing efficient and rapid access to polycyclic scaffolds from readily avail-



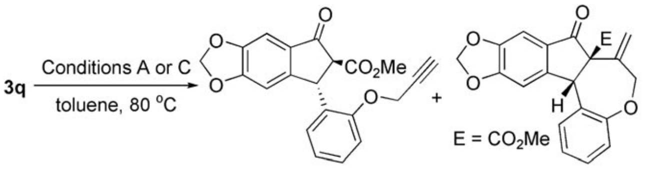
Scheme 2. The 'one-pot' synthetic strategy from β-ketoesters **1** and alkynyl aldehydes **2**, the numbers in parenthesis indicate the isolated yield of the *Z* isomer.



3a **5a**

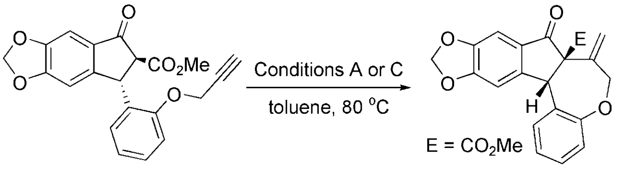
In(OTf)$_3$ (10 mol%), 80 °C	66%
In(OTf)$_3$ (10 mol%), DBU (5 mol%), 80 °C	70%
In(OTf)$_3$ (10 mol%), piperidinium acetate (10 mol%), 80 °C	74%
In(OTf)$_3$ (10 mol%), piperidinium acetate (10 mol%), DBU (5 mol%),100 °C	83%

Scheme 3. Control experiments for the tandem transformation of **3a**.



(1)

	4q	**5q**
Conditions A, 1 h	94%	0
Conditions A, 5 h	70%	trace
Conditions C, 5 h	10%	76% + 10% **3q**
Conditions C, 14 h	0	90%



(2)

	4q	**5q**
Conditions A, 6.5 h		5% + 66% **4q**
Conditions C, 6.5 h		95%

able starting materials. Piperidinium acetate was found to be a catalyst in the one-pot reaction, which may be applicable in other Lewis acid catalyzed reactions. Further studies into the mechanism, synthetic applications, asymmetric catalysis, and development of novel tandem reactions by combining Nazarov cyclization or Conia-ene reactions with other reactions are ongoing in our laboratory.

Acknowledgements

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Keywords: bicyclic compounds · domino reactions · ene reaction · Nazarov cyclization · one-pot reactions · tandem catalysis

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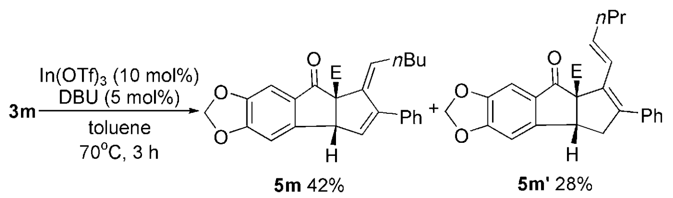
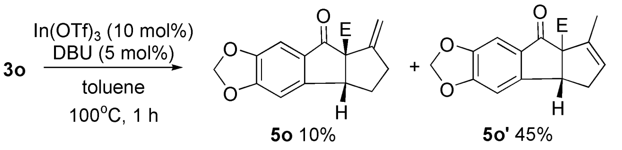
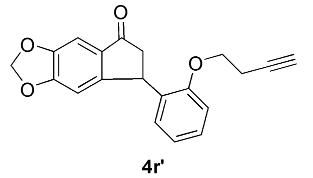


[9] The reaction of **3m** gave the normal product **5m** in 42% yield, along with a 28% yield of **5m'**.

[10] If the reaction of **3o** was quenched after 1 h, a 10% yield of **5o** could be obtained, along with a 45% yield of isomer **5o'** and 10% of **3o** was recovered.

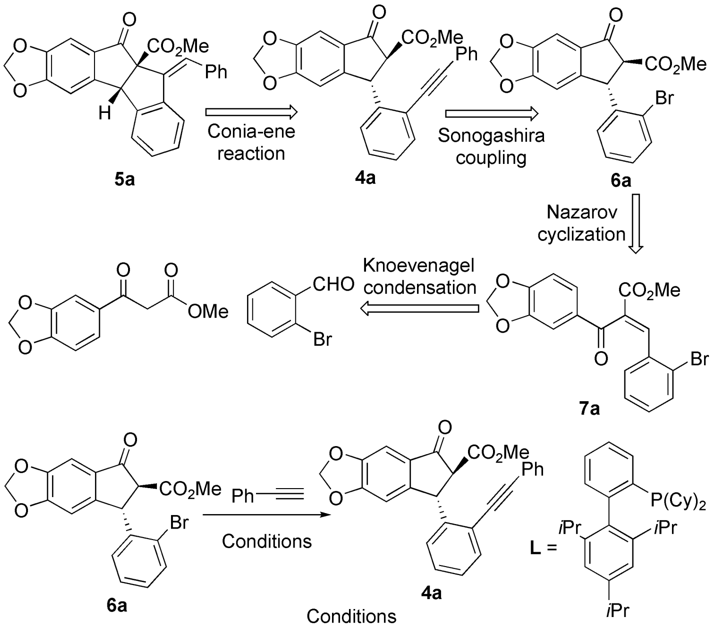


[11] A 15% yield of decarboxylation product **4r'** was produced.



4r'

[12] An alternative stepwise strategy for the synthesis of **5a** was also tested. However, after many attempts, the Sonogashira coupling of **6a** with phenyl acetylene failed under various commonly used conditions. These results indicate that our present one-pot strategy has an advantage over the stepwise strategy.



[Pd(PPh$_3$)$_4$] (5 mol%), CuI (10 mol%), iPr$_2$NH (3 equiv), THF, 50 °C
[Pd(PPh$_3$)$_4$] (5 mol%), CuI (10 mol%), Et$_3$N (solvent), 50 °C
[Pd(PPh$_3$)$_4$] (5 mol%), CuI (10 mol%), Et$_3$N (3 equiv), THF, 30 °C
[Pd(PPh$_3$)$_4$] (5 mol%), CuI (10 mol%), Et$_3$N (3 equiv), CH$_3$CN, 30 °C
Pd(OAc)$_2$ (5 mol%), **L** (10 mol%), K$_3$PO$_4$•3H$_2$O (3 equiv), THF, RT

[13] CCDC-760111 (**5k**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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