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Pt(II)-catalyzed hydroarylation reaction of alkynes with pyrroles and furans

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ABSTRACT

A Pt(II) catalyst showed a drastic effect on hydroarylation of alkynes with pyrroles and furans compared with $Pd(OAc)_2$ catalyst. The hydroarylation reactions proceeded smoothly under mild conditions to give double-hydroarylation products in good yields. Mono-adducts were formed only when the second hydroarylation was inhibited by steric hindrance of substrates or low reactivity of the mono-adducts.

1. Introduction

Heteroarenes are an important class of compounds in organic chemistry because they are incorporated in a wide range of useful organic compounds such as fluorescent dyes, natural products, and pharmaceuticals. Development of their functionalization methods for synthesis of such useful compounds has attracted much attention of many chemists.

Direct C–H bond functionalization is one of the most effective methods in terms of atom-economic and environmentally benign processes because it dose not require pre-functionalization like halogenation.[1] Addition of aromatic C–H bonds to unsaturated C–C bonds is a useful C–H functionalization method for introducing carbon framework onto arenes. To date, it has been reported that some transition metals catalyze addition of heteroarenes to alkynes, affording heteroarylalkenes and bis(heteroaryl)alkanes.[2–9]

We have reported that hydroarylation of alkynes proceeded under mild conditions by using a catalytic amount of $Pd(OAc)_2$ and trifluoroacetic acid (TFA) as solvent to give *cis*-aryl substituted alkenes.[10] The hydroarylation was applied to the reaction of heteroarenes such as pyrroles, indoles, and furans.[4] In the case of heteroarenes, the hydroarylation did not occur in TFA but proceeded in acetic acid or a neutral solvent like CH_2Cl_2 to give heteroarylalkenes in most cases.

Recently, we found that Pt(II) catalysts such as K_2PtCl_4/AgOTf and $PtCl_2$/AgOTf were more effective than $Pd(OAc)_2$ in the hydroarylation of propiolic acids with arenes.[11] Thus, we examined the effect of a more cationic Pt(II) catalyst on the hydroarylation with heteroarenes and found that two molecules of heteroarenes added to the triple bonds. Furthermore, recently published papers[12] let us recognize that this methodology is useful for direct synthesis of *meso*-substituted dipyrromethanes, which are the key building blocks of porphyrinoid macrocycles. Here, we report the Pt(II)-catalyzed double hydroarylation of alkynes with pyrroles and furans.

2. Results and discussion

First of all, we examined the reaction of pyrrole (**1a**, R=H) with ethyl phenylpropiolate (**2a**, R′=Ph) (Eq. 1). The reaction of **1a** (4 mmol) with **2a** (2 mmol) in AcOH (1 mL) was carried out in the presence of K_2PtCl_4 (0.02 mmol) and AgOTf (0.08 mmol) at 30 °C for 9 h to afford ethyl (2*Z*)-3-(pyrrol-2-yl)cinnamate (**3a**) and ethyl 3-phenyl-3,3-di(pyrrol-2-yl)propionate (**4a**) in 4 and 46% yields, respectively (Table 1, entry 1). Double addition of **1a** to the triple bond of **2a** occurred predominantly. This result is in contrast to our previous Pd(II)-catalyzed reaction in which **3a** was obtained exclusively.[4a] It may be attributed to the fact that K_2PtCl_4/AgOTf is a more cationic and active catalyst than $Pd(OAc)_2$.[11b] This interesting result encouraged us to investigate the reaction conditions. The results are listed in Table 1. When the reaction was carried out with 3 equiv of **1a** in the presence of 2% K_2PtCl_4 and 8% AgOTf, **4a** was obtained in 59% yield (entry 2). Use of AgOAc instead of AgOTf retarded the reaction, resulting in the major

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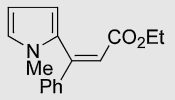
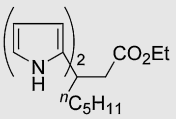
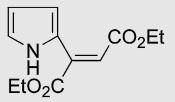
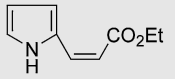
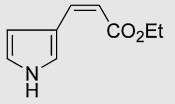
Table 1
Pt(II)-catalyzed hydroarylation of ethyl phenylpropiolate with pyrrole[a]

Entry	Catalyst (%)	Solvent	Time/h	Yield[b]	
				4a/%	**3a**/%
1	K_2PtCl_4/AgOTf (1/4)	AcOH	9	46[c]	4[c]
2	K_2PtCl_4/AgOTf (2/8)	AcOH	11	59[d]	0[d]
3	K_2PtCl_4/AgOAc (2/8)	AcOH	50	16[d]	43[d]
4	K_2PtCl_4/AgOTf (2/8)	AcOH	10	68	0
5	K_2PtCl_4/AgOTf (2/8)	AcOH	20	67[e]	0[e]
6	AgOTf (8)	AcOH	10	No reaction	
7	K_2PtCl_4/AgOTf (2/8)	DCE	12	67	0
8	$(^nBu_4N)_2PtCl_4$ (2)	AcOH	15	60	0
9	$(^nBu_4N)_2PtCl_4$/AgOTf (2/8)	DCE	15	66	0
10	$(^nBu_4N)_2PtCl_4$/AgOAc (2/8)	DCE	50	No reaction	

[a] Reaction conditions: pyrrole (**1a**) (6 mmol), ethyl phenylpropiolate (**2a**) (1 mmol), Pt salt (0.02 mmol), Ag compound (0.08 mmol), and solvent (1 mL) at 30 °C.
[b] Isolated yield based on **2a**.
[c] Compounds **1a** (4 mmol) and **2a** (2 mmol) were used.
[d] Compound **1a** (3 mmol) was used.
[e] AcOH (2 mL) was used.

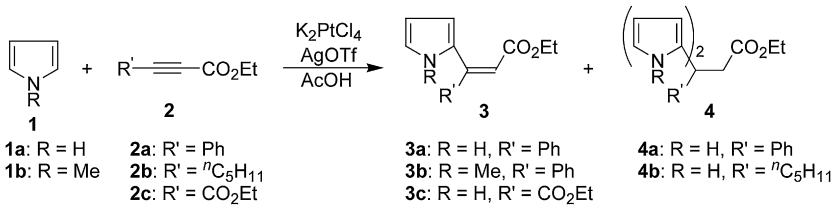
formation of **3a** (Entry 3). The yield of **4a** was improved to be 68% when 6 equiv of **1a** was used (entry 4). The increase of the amount of acetic acid only retarded the reaction rate (entry 5). The reaction did not proceed in the absence of K_2PtCl_4, revealing clearly that a Pt species is an active catalyst in this reaction (entry 6). A neutral solvent, 1,2-dichloroethane (DCE), can be used instead of AcOH, affording **4a** in a similar yield to that in AcOH (entry 7). In order to increase the solubility of catalyst precursor, we examined a soluble Pt(II) salt, $(^nNBu_4)_2PtCl_4$, which was prepared from K_2PtCl_4 and $^nBu_4NCl$. Interestingly, the hydroarylation using $(^nNBu_4)_2PtCl_4$ in AcOH proceeded even in the absence of AgOTf (entry 8). This result reveals that Pt catalyst itself plays an important role in the catalytic cycle and AgOTf is not necessarily required for the reaction. Moreover, $(^nNBu_4)_2PtCl_4$ also catalyzed the reaction in DCE when AgOTf was added (entry 9). These results suggest that Pt precatalyst is activated by AgOTf or by AcOH in the absence of AgOTf. The role of AgOTf is considered to dissolve K_2PtCl_4, which is hardly soluble in organic solvent and to form a more active, cationic Pt species by anion exchange. No reaction took place when AgOAc was added instead of AgOTf (entry 10).

Table 2
Pt(II)-catalyzed hydroarylation of alkynes with pyrroles[a]

Entry	R	**2**	R′	Time/h	Product and yield[b]/%		
1	Me	**2a**	Ph	2		**3b**	71
2	H	**2b**	$^nC_5H_{11}$	24		**4b**	50[c]
3	H	**2c**	EtO_2C	2		**3c**	43
						**3d**	46[d]
4	H	**2d**	H	2		**3e**	22[d]

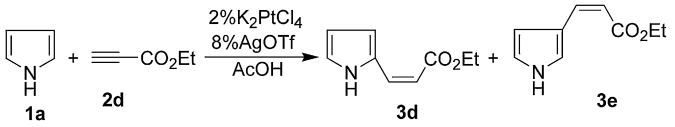
[a] Reaction conditions: a pyrrole (6 mmol), an alkyne (1 mmol), K_2PtCl_4 (0.02 mmol), AgOTf (0.08 mmol), and AcOH (1 mL) at 30 °C.
[b] Isolated yield based on an alkyne.
[c] $Cl(CH_2)_2Cl$ (1 mL) was used instead of AcOH.
[d] NMR yields. Compound **1a** (2 mmol) was used.

(entry 4 and Eq. 2). The low selectivity may be attributed to the higher reactivity of **2d** compared to the other substituted propiolates or the reaction environment.[13] In this reaction, NMR experiments indicated that the elongation of reaction gave an inseparable mixture of double-adducts. For a substituted pyrrole, 2,5-dimethylpyrrole (**1c**), the reaction with **2a** was conducted for 24 h under the conditions of entry 1 in Table 2, but only mono-adduct **3f** was obtained in 48% yield as a mixture of *E*- and *Z*-isomers (3:1).

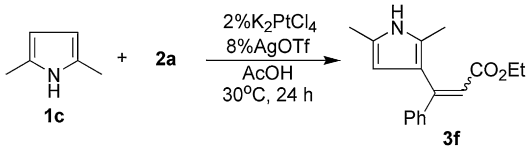


(1)

Next, we examined the reaction of other pyrroles and alkynes (Table 2). Interestingly, the reaction of 1-methylpyrrole (**1b**, R=Me) with **2a** gave mono-adduct **3b** exclusively in 71% yield (entry 1). The result is in contrast with the reaction of **1a** that gives **4a** as a main product. This is probably because the steric hindrance of the methyl group in pyrrole **1b** inhibits the second hydroarylation. The reaction of **1a** with ethyl 2-octynoate (**2b**, R′=$^nC_5H_{11}$) gave double-adduct **4b** in 50% yield (entry 2). The reaction with diethyl acetylenedicarboxylate (**2c**, R′=CO_2Et) gave mono-adduct **3c** in 43% yield (entry 3). The reaction with ethyl propiolate (**2d**, R′=H) gave the regio-isomeric products **3d** and **3e** in 46 and 22% yields, respectively



(2)



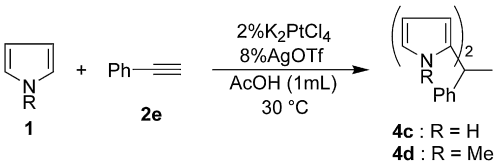
(3)

Table 3
Pt(II)-catalyzed hydroarylation of phenylacetylene with pyrroles[a]

Entry	R	**1**/mmol	Time/h	Product	Yield[b]/%
1	H	10	20	**4c**	65
2	Me	10	20	**4d**	65
3	Me	6	20	**4d**	45
4	Me	6	21	**4d**	0[c]

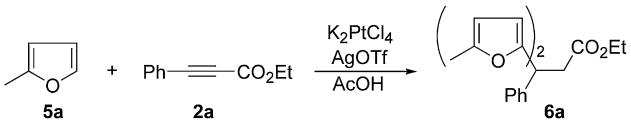
[a] Reaction conditions: a pyrrole **1**, phenylacetylene (**2e**) (1 mmol), K_2PtCl_4 (0.02 mmol), AgOTf (0.08 mmol), and AcOH (1 mL) at 30 °C.
[b] Isolated yield based on **2e**.
[c] Without K_2PtCl_4/AgOTf.

Phenylacetylene (**2e**) also participated in the reaction as well as propiolates (Eq. 4 and Table 3). The reactions of **1a** and **1b** gave the corresponding double-adducts **4c** and **4d** in good yields, respectively, although a large amount of a pyrrole was required (entries 1 and 2). Use of 6 equiv of **1b** resulted in an inferior yield (entry 3). Again, no products were formed in the absence of K_2PtCl_4/AgOTf (entry 4).



(4)

The reaction was applied to furans like 2-methylfuran (**5a**) and 2,5-dimethylfuran (**5b**). The reaction of **5a** with **2a** proceeded under the same reaction conditions to give a double-adduct, ethyl 3,3-bis(4-methylfur-2-yl)-3-phenylpropionate (**6a**) in 78% yield (Eq. 5 and entry 1, Table 4). This result is completely different from that of the corresponding $Pd(OAc)_2$ catalyzed reaction where mono-adduct is formed.[4a] $(^nBu_4N)_2PtCl_4$ did not catalyze the reaction of furan effectively, resulting in almost no reaction (entry 2) because of lower reactivity of a furan. Again, AgOTf does not catalyze the reaction, suggesting that an active species in the reaction is a Pt species (entry 3).



(5)

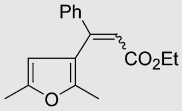
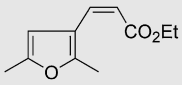
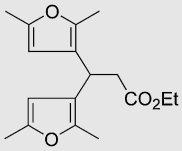
The reactions of **5b** with alkynes **2** were also examined (Eq. 6 and Table 5). The reaction of **2a** with **5b** gave mono-addition product **7a** in 80% yield (entry 1). In this case, the product was obtained as a mixture of the stereoisomers (*E*/*Z*=1.3:1). No double-adduct was observed probably due to the steric reason. In the case of **2d**, the reaction of **5b** in the presence of 1% K_2PtCl_4 and 4% AgOTf gave mono-adduct **7b** selectively (entry 2). The second addition reaction of **5b** to mono-adduct **7b** is slow under the reaction conditions and requires a higher reaction temperature. Actually, the second addition of **5b** occurred to afford double-adduct **6b** as a main product when the reaction was carried out at 50 °C (entry 3). In the reaction of **2b** with **5a**, hydroarylation did not take place, resulting in the formation of ethyl 2-oxooctanoate by hydration of **2b**. The reactions of **2c** did not afford any hydroarylation products although a small amount of Diels–Alder adducts **8a** and **8b** was isolated (Eq. 7). These results are explained by low reactivity of furans for hydroarylation compared with pyrroles.

Table 4
Pt(II)-catalyzed hydroarylation of ethyl phenylpropiolate with 2-methylfuran[a]

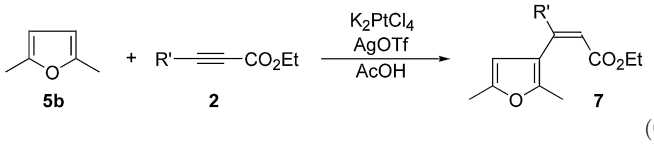
Entry	Catalyst (%)	Solvent	**5a**/mmol	Time/h	Yield of **6a**[b]/%
1	K_2PtCl_4/AgOTf (2/8)	AcOH	6	12	90
2	$(^nBu_4N)_2PtCl_4$ (2)	AcOH	6	120	8
3	AgOTf (8)	AcOH	6	45	0

[a] Reaction conditions: 2-methylfuran (**5a**), ethyl phenylpropiolate (**2a**) (1 mmol), catalyst, and solvent (1 mL) at 30 °C.
[b] Isolated yield based on **2a**.

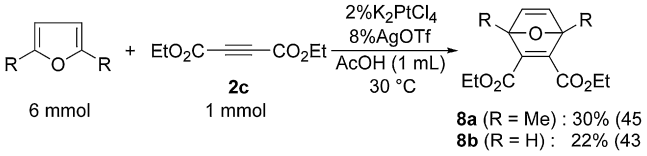
Table 5
Pt(II)-catalyzed hydroarylation of alkynes with 2,5-dimethylfurans[a]

Entry	**5b**/mmol	**2**	R	Time/h	Product and yield[b]/%
1	6	**2a**	Ph	48	 **7a** 80 (*Z*/*E*=1.3/1)
2	12	**2d**	H	40	 **7b** 62[c]
3	10	**2d**	H	40	 **6b** 51[d,e]

[a] Reaction Conditions: 2,5-dimethylfuran (**5b**), an alkyne **2** (1 mmol), K_2PtCl_4 (0.02 mmol), AgOTf (0.08 mmol), and AcOH (1 mL) at 30 °C.
[b] Isolated yield based on **2**.
[c] Ethyl propiolate (2 mmol) was used.
[d] Temperature 50 °C.
[e] Compound **7b** was formed in 10% yield.

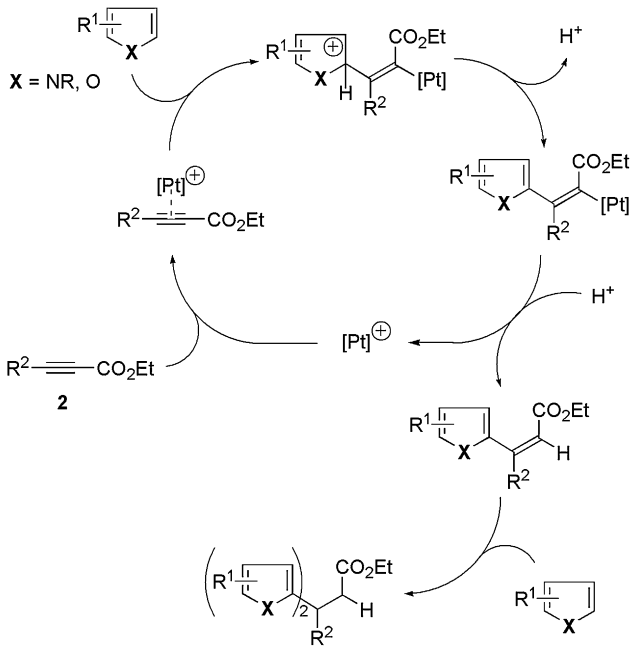


(6)



(7)

The hydroarylation is considered to proceed via electrophilic aromatic substitution mechanism. The mechanism is illustrated in Scheme 1. An alkyne is activated by the coordination of an active Pt(II) catalyst derived from a Pt precursor, followed by attack to a heteroarene electrophilically to form a Wheland intermediate. Proton release followed by protonation of the resulting intermediate affords a heteroarylalkene. The second hydroarylation of the forming heteroarylalkene leading to a bis(heteroaryl)alkane is also considered to proceed in the same way. In some cases, the reactions gave mono-adducts exclusively. This is explained by the steric and electronic reasons. In the case of the reaction of **2a** with **1b** or **5b**, steric hindrance at the β-position of the resulting cinnamate probably inhibits the second hydroarylation because methyl group is present at the 2-position of the heteroaryl group. In the case of **2c**, the second hydroarylation is considered to be prevented because mono-adduct **3c** is an electron-deficient alkene, which is less reactive for the hydroarylation. The heteroarylalkenes obtained from the hydroarylation are usually electron-rich alkenes and reactive enough to undergo the second hydroarylation. This is consistent with the fact that the reaction of pyrrole with less electron-rich alkenes, ethyl cinnamates, did not take place.



Scheme 1. The plausible reaction mechanism.

3. Conclusion

We have demonstrated that Pt(II) catalysts showed a drastic effect on the hydroarylation of alkynes with pyrroles and furans. The Pt(II) catalysts like K_2PtCl_4/AgOTf is revealed to catalyze the hydroarylation effectively to give double-hydroarylation products in good yields. Mono-adducts were obtained predominantly when second hydroarylation was inhibited by steric hindrance of substrates or low reactivity of forming mono-adducts.

4. Experimental

4.1. General

All solvents and reagents were commercially available and used as received without further purification. $(^nNBu_4)_2PtCl_4$ was prepared from K_2PtCl_4 and $^nBu_4NCl$ according to the reported method.[14] All reactions were conducted in a dry Pyrex tube with a rubber septum. In the cases of furans, the reactions were conducted in the tube with screw cap. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL 300 FT-NMR using tetramethylsilane (TMS) as internal standard. Melting points were measured with YANACO micro melting apparatus and are uncorrected. Mass spectra were measured on a Shimadzu GC/MS 5020A. Elemental analyses were performed by the Service Center of the Elementary Analysis of Organic Compounds, Faculty of Science, Kyushu University.

4.2. General procedure for the K_2PtCl_4/AgOTf-catalyzed hydroarylation of alkynes with pyrroles or furans. Typical example: the reaction of pyrrole with ethyl phenylpropiolate (Table 1, entry 3)

After a mixture of K_2PtCl_4 and AgOTf in acetic acid was stirred for 1 h, pyrrole (6 mmol) and ethyl phenylpropiolate (1 mmol) were added to the mixture. The reaction was monitored by TLC. After the reaction, the reaction mixture was poured into water, neutralized by $NaHCO_3$, and extracted with CH_2Cl_2 (10 mL×4). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography with a mixture of AcOEt/hexane as eluent to give **4a** in 68% yield.

4.2.1. Ethyl (2Z)-3-(1H-pyrrol-2-yl)cinnamate (**3a**)[4a]

Light yellow liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J=7.1 Hz, 3H, CH_3), 4.23 (q, J=7.1 Hz, 2H, OCH_2), 5.58 (s, 1H, vinyl), 6.09 (m, 1H, pyrrolyl), 6.21 (m, 1H, pyrrolyl), 7.07 (m, 1H, pyrrolyl), 7.35–7.42 (m, 5H, Ph), 12.96 (br s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.26, 60.60, 109.71, 109.74, 118.97, 122.82, 127.78, 128.16, 128.86, 130.31, 142.50, 149.18, 168.89.

4.2.2. Ethyl (2Z)-3-(1-methyl-1H-pyrrol-2-yl)cinnamate (**3b**)[4a]

Light yellow liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, J=7.1 Hz, 3H, CH_3), 3.32 (s, 3H, Me), 4.11 (q, J=7.1 Hz, 2H, OCH_2), 6.12 (dd, J=1.8, 3.7 Hz, 1H, pyrrolyl), 6.19 (dd, J=2.6, 3.7 Hz, 1H, pyrrolyl), 6.37 (s, 1H, vinyl), 6.73 (dd, J=1.8, 2.6 Hz, 1H, pyrrolyl), 7.31–7.35 (m, 5H, Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.14, 34.34, 60.04, 107.74, 111.60, 118.83, 123.69, 127.98, 128.42, 129.51, 129.85, 140.36, 147.03, 165.95.

4.2.3. Diethyl (2Z)-2-(1H-pyrrol-2-yl)fumarate (**3c**)[15]

Yellow liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, J=7.1 Hz, 3H, CH_3), 1.38 (t, J=7.1 Hz, 3H, CH_3), 4.24 (q, J=7.1 Hz, 2H, OCH_2), 4.36 (q, J=7.1 Hz, 2H, OCH_2), 5.94 (s, 1H, vinyl), 6.29 (m, 1H, pyrrolyl), 6.73 (m, 1H, pyrrolyl), 7.04 (m, 1H, pyrrolyl), 12.60 (br s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.09, 14.11, 61.13, 61.99, 110.08, 110.47, 117.84, 123.59, 125.94, 139.04, 167.80, 168.58. MS (EI, m/z (relative intensity)): 237 (M^+, 98), 192 (18), 191 (17), 165 (58), 136 (20), 119 (30), 91 (100).

4.2.4. Ethyl (2Z)-3-(1H-pyrrol-2-yl)acrylate (**3d**)[4a]

Light yellow liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J=7.1 Hz, 3H, CH_3), 4.21 (q, J=7.1 Hz, 2H, OCH_2), 5.52 (d, J=12.6 Hz, 1H, vinyl), 6.26 (m, 1H, pyrrolyl), 6.50 (m, 1H, pyrrolyl), 6.76 (d, J=12.6 Hz, 1H, vinyl), 6.99 (m, 1H, pyrrolyl), 12.24 (br s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.24, 60.39, 107.67, 110.09, 118.54, 122.87, 129.09, 134.66, 169.18.

4.2.5. Ethyl (2Z)-3-(1H-pyrrol-3-yl)acrylate (**3e**)

Yellow liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, J=7.1 Hz, 3H, CH_3), 4.20 (q, J=7.1 Hz, 2H, OCH_2), 5.62 (d, J=12.6 Hz, 1H, vinyl), 6.70 (m, 1H, pyrrolyl), 6.74 (m, 1H, pyrrolyl), 6.82 (d, J=12.6 Hz, 1H, vinyl), 7.75 (m, 1H, pyrrolyl), 8.57 (br s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.33, 59.64, 111.80, 112.27, 118.15, 119.65, 123.99, 138.33, 167.07. Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.20; H, 6.75; N, 8.36.

4.2.6. Ethyl 3-(2,5-1H-pyrrol-3-yl)cinnamate (E/Z=3:1) (**3f**)

Yellow crystals. Mp 84–85 °C (CH_2Cl_2/hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (t, J=7 Hz, CH_3), 1.26 (t, J=7 Hz, CH_3), 1.78 (s, CH_3), 1.93 (s, CH_3), 2.15 (s, CH_3), 2.19 (s, CH_3), 3.99 (q, J=7 Hz, CH_3), 4.15 (q, J=7 Hz, CH_3), 5.68 (s, =CH), 5.77 (s, =CH), 6.03 (s, ArH), 6.07 (s, ArH), 7.21–7.25 (m, ArH), 7.30–7.40 (m, ArH), 7.74 (br s, NH), 7.79 (br s, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.35, 12.54, 12.78, 13.17, 13.98, 14.28, 59.30, 59.60, 106.8, 108.52, 111.56, 114.87, 117.56, 120.76, 125.08, 125.98, 127.18, 127.36, 127.57, 127.92, 128.31, 128.44, 128.61, 128.75, 140.51, 142.72, 152.71, 153.99, 166.54, 167.04. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.64; H, 7.16; N, 5.20.

4.2.7. Ethyl 3-phenyl-3,3-di(1H-pyrrol-2-yl)propionate (**4a**)

Colorless crystals. Mp 123–125 °C (CH_2Cl_2/hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (t, J=7.1 Hz, 3H, CH_3), 3.59 (s, 2H, CH_2CO), 4.06 (q, J=7.1 Hz, 2H, OCH_2), 5.69 (m, 2H, pyrrolyl), 6.11 (m, 2H, pyrrolyl), 6.70 (m, 2H, pyrrolyl), 6.98–7.01 (m, 2H, Ph), 7.21–7.29 (m, 3H, Ph), 9.05 (br s, 2H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.95,

46.14, 46.89, 61.10, 107.50, 107.59, 117.27, 126.86, 127.32, 128.07, 135.57, 145.97, 173.31. MS (EI, *m*/*z* (relative intensity)): 308 (M^+, 21), 221 (100), 154 (15), 110 (9). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.16; H, 6.55; N, 9.15.

*4.2.8. Ethyl 3,3-bis(1H-pyrrol-2-yl)octanoate (**4b**)*

Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, J=6.6 Hz, 3H, CH_3), 1.16 (t, J=7.1 Hz, 3H, CH_3), 1.25 (m, 6H, CH_2), 2.05 (m, 2H, CH_2), 3.01 (s, 2H, CH_2CO), 4.03 (q, J=7.1 Hz, 2H, OCH_2), 6.00 (m, 2H, pyrrolyl), 6.12 (m, 2H, pyrrolyl), 6.64 (m, 2H, pyrrolyl), 8.55 (br s, 2H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.98, 14.01, 22.47, 24.07, 32.12, 40.86, 41.77, 43.54, 60.63, 105.29, 107.64, 116.92, 135.45, 172.73. MS (EI, *m*/*z* (relative intensity)): 302 (M^+, 24), 231 (100), 215 (41), 185 (20), 157 (8), 143 (7), 94 (9), 92 (14). Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.39; H, 8.64; N, 9.23.

4.2.9. 1,1-Bis(1H-pyrrol-2-yl)-1-phenylethane (4c).[16]

Light orange crystals. Mp 114–117 °C (CH_2Cl_2/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (s, 3H, CH_3), 5.97 (m, 2H, pyrrolyl), 6.17 (m, 1H, pyrrolyl), 6.65 (m, 1H, pyrrolyl), 7.09–7.13 (m, 2H, Ph), 7.19–7.30 (m, 3H, Ph), 7.76 (br s, 2H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.84, 44.76, 106.30, 108.26, 116.87, 126.66, 127.41, 128.16, 137.46, 147.28. MS (EI, *m*/*z* (relative intensity)): 236 (M^+, 36), 221 (100), 154 (31), 110 (17), 92 (12).

*4.2.10. 1,1-Bis(1-methyl-1H-pyrrol-2-yl)-1-phenylethane (**4d**)*

Yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.08 (s, 3H, CH_3), 3.09 (s, 6H, CH_3), 5.86 (dd, J=2.1, 3.6 Hz, 1H, pyrrolyl), 6.02 (dd, J=3.0, 3.6 Hz, 1H, pyrrolyl), 6.55 (dd, J=2.1, 3.0 Hz, 1H, pyrrolyl), 7.11–7.14 (m, 2H, Ph), 7.21–7.31 (m, 3H, Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 29.76, 35.24, 45.00, 105.90, 109.23, 123.57, 126.34, 127.81, 127.88, 136.96, 146.99. MS (EI, *m*/*z* (relative intensity)): 264 (M^+, 49), 249 (100). The regiochemistry of the compound was determined by NOE experiments. Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.94; H, 7.55; N, 10.32.

*4.2.11. Ethyl 3,3-bis(5-methylfur-2-yl)-3-phenylpropionate (**6a**)*

Light yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (t, J=7.1 Hz, 3H, CH_3), 2.25 (s, 6H, CH_3), 3.40 (s, 2H, CH_2CO), 4.00 (q, J=7.1 Hz, 2H, OCH_2), 5.90 (d, J=3.0 Hz, 2H, furyl), 5.93 (d, J=3.0 Hz, 2H, furyl), 7.11–7.15 (m, 2H, Ph), 7.21–7.29 (m, 3H, Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.61, 13.92, 43.10, 48.92, 60.15, 106.01, 108.98, 126.82, 127.56, 127.91, 143.46, 151.18, 154.25, 170.25. MS (EI, *m*/*z* (relative intensity)): 338 (M^+, 4), 252 (23), 251 (100), 208 (4), 179 (4), 178 (4), 165 (6), 118 (9). Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.45; H, 6.61.

*4.2.12. Ethyl 3,3-bis(2,5-dimethylfur-3-yl)propionate (**6b**)*

Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, J=7.1 Hz, 3H, CH_3), 2.18 (s, 6H, CH_3), 2.19 (s, 6H, CH_3), 2.70 (d, J=7.8 Hz, 2H, CH_2CO), 4.05 (q, J=7.1 Hz, 2H, OCH_2), 4.07 (t, J=7.8 Hz, 1H, CH), 5.84 (s, 2H, furyl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.47, 13.47, 14.05, 28.88, 41.12, 60.23, 105.34, 121.52, 144.72, 149.44, 171.80. IR (neat, cm^{-1}) 2982, 2922, 1736 (C=O), 1639, 1582, 1442, 1372, 1259, 1222, 1172, 1037, 798. MS (EI, *m*/*z* (relative intensity)): 290 (M^+, 24), 203 (100), 173 (13), 159 (22), 121 (25), 91 (10). Contamination of a trace amount of impurities did not give a satisfactory analysis.

*4.2.13. Ethyl (2Z)-3-(2,5-dimethylfur-3-yl)cinnamate (**7a**-Z)*

Slightly yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J=7.1 Hz, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 4.16 (q, J=7.1 Hz, 2H, OCH_2), 5.83 (s, 1H, furyl), 6.21 (s, 1H, vinyl), 7.33–7.37 (m, 5H, Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.80, 13.41, 14.24, 59.97, 108.55, 117.54, 118.22, 128.16, 128.31, 129.24, 140.92, 149.19, 149.29, 149.54, 165.89. MS (EI, *m*/*z* (relative intensity)): 270 (M^+, 97), 253 (66), 227 (100), 225 (69), 199 (58), 195 (65), 182 (58), 181 (62), 153 (61), 152 (52), 128 (26), 115 (26), 91 (20), 77 (29). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.20; H, 6.73. Compound **7a** was obtained as a mixture of *Z*- and *E*-stereoisomers. The *Z*-isomer of **7a** was partially isolated from the mixture of the stereoisomers by column chromatography. The stereochemistry of **7a** was determined by NOE experiments.

*4.2.14. Ethyl (2E)-3-(2,5-dimethylfur-3-yl)cinnamate (**7a**-E)*

Colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (t, J=7.1 Hz, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 4.01 (q, J=7.1 Hz, 2H, OCH_2), 5.92 (s, 1H, furyl), 6.05 (s, 1H, vinyl), 7.19–7.22 (m, 2H, Ph), 7.34–7.36 (m, 2H, Ph). MS (EI, *m*/*z* (relative intensity)): 270 (M^+, 97), 253 (66), 227 (100), 225 (74), 199 (58), 195 (63), 182 (57), 181 (62), 153 (63), 152 (51), 128 (25), 115 (26), 91 (20), 77 (31). The *E*-isomer of **7a** could not be separated from a mixture of the *Z*- and *E*-stereoisomers.

*4.2.15. Ethyl (2Z)-3-(2,5-dimethylfur-3-yl)acrylate (**7b**)*[17]

Light yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, J=7.1 Hz, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.20 (q, J=7.1 Hz, 2H, OCH_2), 5.65 (d, J=12.6 Hz, 1H, vinyl), 6.63 (d, J=12.6 Hz, 1H, vinyl), 6.82 (s, 1H, furyl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.79, 13.16, 14.23, 59.82, 107.30, 114.15, 117.63, 133.79, 149.84, 154.36, 166.46. MS (EI, *m*/*z* (relative intensity)): 194 (M^+, 100), 165 (61), 149 (77), 123 (42), 119 (42), 91 (55), 77 (57). IR (neat, cm^{-1}) 2983, 1718 (C=O), 1627, 1176, 1444, 1399, 1030.

*4.2.16. Diethyl 1,4-dimethyl-7-oxabicyclo[2,2,1]hepta-2,5-diene-2,3-dicarboxylate (**8a**)*[18]

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, J=7.1 Hz, 6H, CH_3), 1.80 (s, 6H, CH_3), 4.25 (q, J=7.1 Hz, 4H, OCH_2), 6.95 (s, 2H, vinyl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.08, 15.36, 61.14, 92.00, 147.22, 154.49, 164.04.

*4.2.17. Diethyl 7-oxabicyclo[2,2,1]hepta-2,5-diene-2,3-dicarboxylate (**8b**)*[18]

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J=7.1 Hz, 6H, CH_3), 4.27 (q, J=7.1 Hz, 4H, OCH_2), 5.68 (m, 2H, H1 and H4), 7.22 (m, 2H, vinyl). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.06, 61.38, 85.06, 143.21, 152.66, 163.03.

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