Ring Transformation of Fused Pyridazines. III.[1] 1-Substituted Phthalazines with Ynamines

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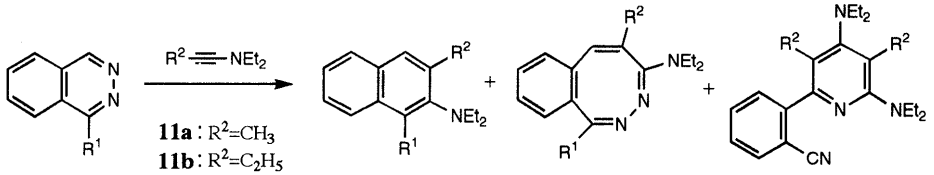
In the reaction of 1-substituted phthalazines with ynamines, there are three patterns of ring transformation, giving naphthalene derivatives through addition–cyclization–denitrogenation (type A), giving benzodiazocine derivatives through addition–cyclization–ring expansion (type B), and giving penta-substituted pyridine derivatives through N–N bond cleavage of the pyridazine ring (type C). In these reactions, it is considered that the substituent group at the 1-position of the phthalazine ring is a significant factor determining the outcome.

Key words 1-substituted phthalazine; ring transformation; substituent effect; ynamine

It is well known that heteroaromatic systems that possess electron-deficient azadienes are suited for participation in inverse-electron-demand Diels–Alder reactions. The recognition of the electron-deficient nature of heteroaromatic azadienes led to their application in this way. We have reported that phthalazine derivatives having an electron-withdrawing substituent such as a nitrile or tosyl group react with ynamines to give naphthalene derivatives through addition–cyclization–denitrogenation.[1] In contrast, 1-chlorophthalazine reacts with ynamines to give penta-substituted pyridine derivatives through N–N bond cleavage of the pyridazine ring.[2] In this paper, we report



starting material	LUMO level (eV)[4]	R¹	R²	yield(%) type A	type B	type C
1	-0.87169	OCH_3	CH_3	-	-	-[1]
2	-1.01569	H	CH_3	-	-	-
3	-1.04735	C_6H_5	CH_3	-	-	-
4	-1.10352	SCH_3	CH_3	-	-	-[1]
5	-1.14187	$NHCOCH_3$	CH_3	-	-	-
6	-1.20526	Cl	CH_3	-	-	**6c** (68)[2]
			CH_2CH_3	-	-	**6c'** (35)[2]
7	-1.46598	COC_6H_5	CH_3	**7a** (42)	**7b** (37)	-
			CH_2CH_3	**7a'** (38)	**7b'** (38)	-
8	-1.34660	$CONH_2$	CH_3	**8a** (61)	-	-
9	-1.63559	CN	CH_3	**9a** (90)[3]	-	-
10	-1.38970	Ts	CH_3	**10a** (57)[1]	-	-
			CH_2CH_3	**10a'** (31)[1]	-	-

Chart 1

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the limitations of the reaction with ynamines and the substituent effect at the 1-position of the phthalazine ring in the reaction with ynamines.

The electron-withdrawing properties of COPh and $CONH_2$ groups are intermediate between those of Cl and tosyl (Ts) groups. First, to investigate the substituent effect, we examined the reactivity with ynamines of phthalazine derivatives, substituted at the 1-position. 1-Phthalazinecarboxamide (**8**) reacted with ynamine to give the naphthalene derivative with denitrogenation, as observed in 1-phthalazinecarbonitrile (**9**) and 1-tosylphthalazine (**10**). On the other hand, 1-benzoylphthalazine (**7**) reacted with ynamines to give not only benzodiazocine derivatives with ring expansion but also naphthalene derivatives. The data are summarized in Chart 1.

It is considered that the substituent group at the 1-position of the phthalazine ring plays two roles in these reactions. The first step of the reaction is attack at the 4-position of the phthalazine ring (most electrophilic site) by the nucleophilic carbon of the ynamines. As shown in Chart 1, phthalazine (**2**), 1-phenylphthalazine[5] (**3**) and 1-acetamidophthalazine[6] (**5**) bearing a substituent with electronic properties intermediate between those of Cl and OCH_3 groups did not react with ynamines which have a high level of LUMO. These results suggest that the addition of ynamines to the 4-position of phthalazine derivatives is controlled by the interaction between the ynamine's HOMO and the LUMO of the phthalazine derivatives. What governs the LUMO of phthalazine derivatives is the substituent effect at the 1-position of the phthalazine ring; electron-withdrawing groups lead to a significant decrease in the LUMO energy of phthalazine derivatives and allow easy attack at the 4-position of the phthalazine ring. In short, the substituent at the 1-position of the phthalazine ring determines the ease of addition of ynamine, *i.e.*, the first step in the reaction.

The other important role of the substituent at the 1-position of the phthalazine ring concerns the reaction pathway. Addition of ynamine to phthalazine derivatives generates a ketene-immonium ion that is very reactive.[7] It is thought that the factor that decides what neutralizes the ketene-immonium ion is the electronic property of the substituent at the 1-position. A Ts, CN, $CONH_2$ or COPh group will tend to neutralize the ketene-immonium ion at the 1-position through the conjugated system, and particularly in the case of COPh group, at the 3-position as well. In 1-chlorophthalazine, due to the +M effect of chlorine, the neutralization of the ketene-immonium ion is achieved not by the pyridazine moiety as observed in **7**—**10** but preferentially by another molecule of ynamine.

It has been reported by us that 2-phenyl-7-(*p*-tolylsulfonyl)thiazolo[4,5-*d*]pyridazine (**12**) reacts with ynamine to give diazocine derivatives together with a naphthalene derivative,[1] as observed with 1-benzoylphthalazine. The fact that 1-tosylphthalazine, whose fused ring is different from that of **12**, reacts with ynamine to give only the naphthalene derivative implies an influence of the fused ring on the reaction path. So, to investigate the substituent effect in the benzene ring upon the reaction, we introduced a methoxy group (electron-donating group)

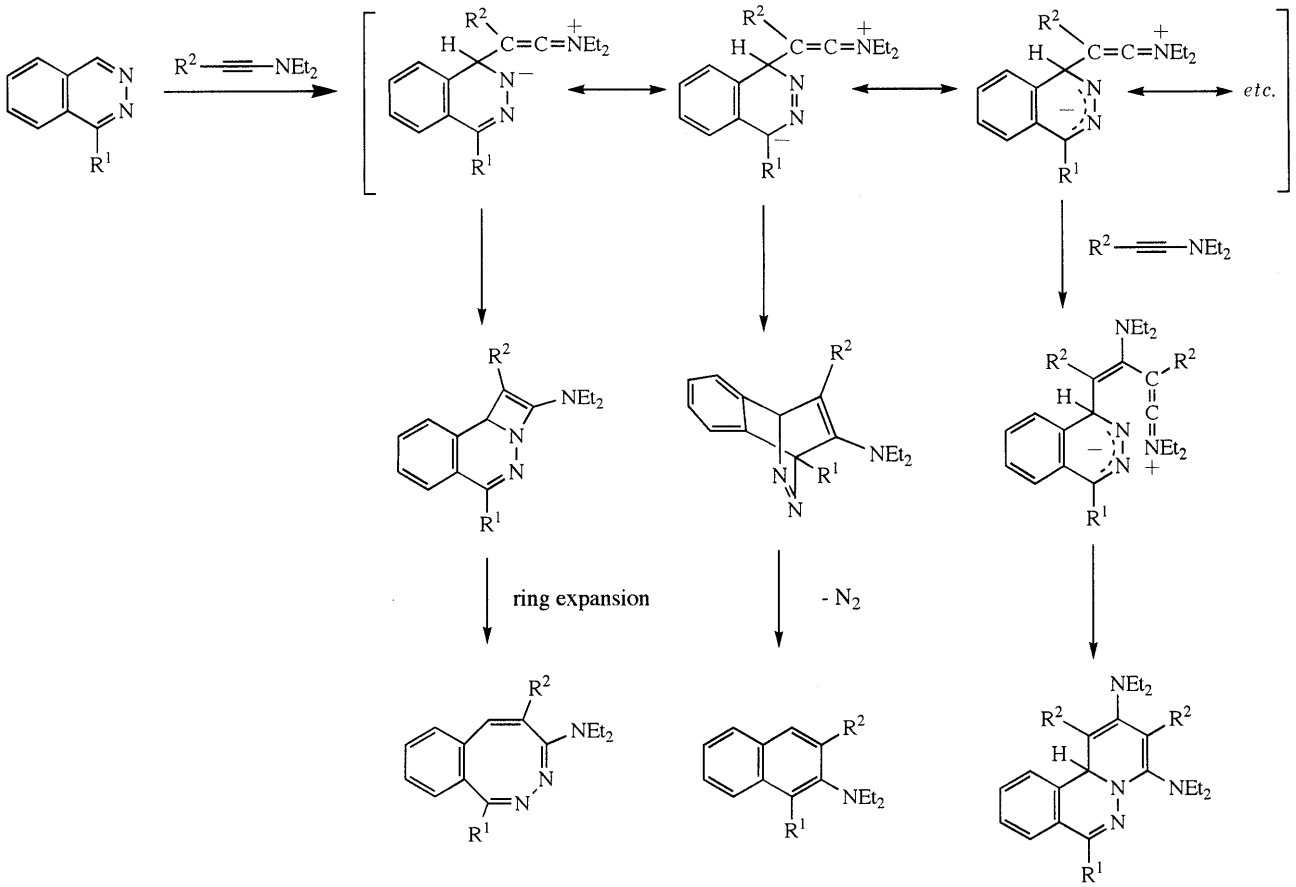

Chart 2

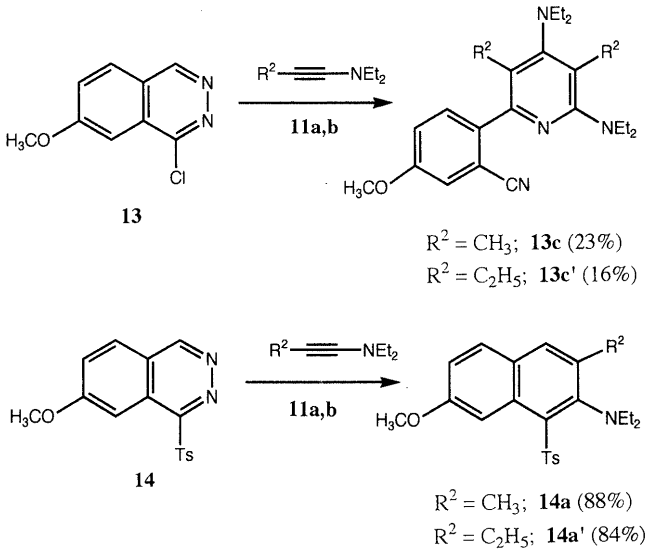

Chart 3

at the 7-position of 1-chloro or 1-tosylphthalazine, and examined the reaction with ynamine. As shown in Chart 3, a methoxy group at the 7-position did not affect the reaction patterns.

The result suggests that the methoxy group at the 7-position of the phthalazine ring does not influence the localization of electrons in the pyridazine ring. The way in which the fused ring influences the reaction pattern is under further investigation.

In conclusion, the substituent at the 1-position of phthalazine plays a significant role in determining the reaction patterns in the reaction with ynamines. A consideration of the electronic properties of the substituent at the 1-position of phthalazine may allow us to predict which reaction will proceed preferentially.

Experimental

All melting points are uncorrected. IR spectra were taken with a JASCO A-102 diffraction grating IR spectrometer. ^{1}H-NMR spectra were measured at 60 MHz on a Hitachi R-24B high-resolution NMR spectrometer and at 270 MHz on a JEOL instrument, and ^{13}C-NMR spectra were obtained with a JEOL JNM-FX90Q FTNMR spectrometer. Chemical shifts are expressed in parts per million (ppm) with tetramethylsilane as an internal standard. Abbreviations of ^{1}H-NMR signal patterns are as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Mass spectra were recorded with a JEOL JMS D-100 mass spectrometer. Column chromatography was carried out on silica gel (Merck Co.Ltd., 200 mesh).

1-Phthalazinecarboxamide (8) 1-Phthalazinecarbonitrile[8] (**9**) (300 mg, 1.93 mmol) was dissolved in acetone (20 ml), 15% K_2CO_3 (6 ml) and 30% H_2O_2 (12 ml) were added, and the mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was extracted with $CHCl_3$ twice. The organic layer was washed with water and brine, and then dried over Na_2SO_4. The solvent was evaporated *in vacuo*, and the residue was chromatographed (silica gel, $CHCl_3$–C_6H_6) to give **8** (81 mg, 24%) as pale yellow prisms from MeOH. *Anal.* Calcd for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.26. Found: C, 62.52; H, 4.20; N, 24.52. IR (KBr): 3300, 3200, 1680 cm^{-1}.

7-Methoxy-1-tosylphthalazine (14) A solution of 1-chloro-7-methoxyphthalazine[9] (**13**) (1 g, 5.14 mmol) and *p*-toluenesulfinic acid sodium salt (1.83 g, 10.3 mmol) in *N*,*N*-dimethylformamide (DMF) (42 ml) was heated at 100 °C for 2 h. The reaction was quenched with water and the mixture was extracted with $CHCl_3$ twice. The combined organic extract was washed with water and brine, and dried over Na_2SO_4. The solvent was evaporated, and the residue was chromatographed (silica gel, $CHCl_3$–C_6H_6) to give 7-methoxy-1-tosylphthalazine (**14**) as colorless needles from benzene in 63% yield (1.02 g). *Anal.* Calcd for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.49; N, 8.91. Found: C, 61.27; H, 4.51; N, 9.11. IR (KBr): 1330, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 9.36 (1H, s), 8.35 (1H, d, J=2.6 Hz), 8.03—7.98 (2H, m), 7.94 (1H, d, J=8.8 Hz), 7.59 (1H, dd, J=8.8, 2.6 Hz), 7.42—7.39 (2H, m), 4.10 (3H, s), 2.47 (3H, s). ^{13}C-NMR ($CDCl_3$): 163.5, 158.8, 152.2, 145.5, 134.7, 129.9, 129.8, 129.1, 126.2, 124.7, 123.7, 102.6, 56.3, 21.8.

Reaction of Phthalazine Derivatives (7, 8, 13, 14) with Ynamines (11a, b) The procedure for the reaction of 1-phthalazinecarboxamide (**8**) with *N*,*N*-diethyl-1-propynylamine (**11a**) is described as a typical example.

11a (283 mg, 2.54 mmol) was added to a solution of **8** (200 mg, 1.15 mmol) in dioxane (4 ml), and the mixture was heated at 80 °C for 10 min with stirring and then allowed to cool. Water was added, and the reaction mixture was neutralized with diluted HCl and extracted with $CHCl_3$. The organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed (silica gel, benzene) to give 2-diethylamino-3-methylnaphthalenecarboxamide (**8a**) as colorless needles from benzene–hexane in 61% yield (180 mg), mp 130—132 °C. *Anal.* Calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.86; H, 8.05; N, 10.79. MS *m/z*: 256 (M^+). IR (KBr): 3400, 3200, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 7.92—7.88 (1H, m), 7.71—7.66 (1H, m), 7.63 (1H, s), 7.45—7.35 (2H, m), 6.33 (1H, br), 5.81 (1H, br), 3.20 (4H, q), 2.45 (3H, s), 1.09 (6H, t). ^{13}C-NMR ($CDCl_3$): 172.3, 144.8, 136.8, 133.5, 131.3, 130.7, 129.5, 126.9, 126.0, 125.5, 124.6, 47.7, 20.1, 14.5.

From the reaction of 1-benzoylphthalazine[10] (**7**) (300 mg, 1.28 mmol) with **11a** (313 mg, 2.82 mmol), 1-benzoyl-2-diethylamino-3-methylnaphthalene (**7a**) was obtained as a pale green oil in 42% yield (171 mg) from the first fraction eluted with hexane. MS *m/z*: 317 (M^+). IR (neat): 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 7.77—7.68 (4H, m), 7.55—7.47 (2H, m), 7.41—7.27 (4H, m), 3.14—2.68 (4H, m), 2.46 (3H, s), 0.94—0.35 (6H, m). ^{13}C-NMR ($CDCl_3$): 199.5, 146.2, 139.3, 136.7, 136.4, 132.7, 131.4, 131.0, 130.2, 129.1, 128.3, 127.0, 125.9, 125.5, 124.6, 47.8, 20.2, 13.7. 1-Benzoyl-4-diethylamino-5-methyl-2,3-benzodiazocine (**7b**) was obtained as yellow prisms in 37% yield (165 mg) from the second fraction eluted with hexane/AcOEt=10/1, mp 127—128 °C (ether). *Anal.* Calcd for $C_{22}H_{23}N_3O$: C, 76.49; H, 6.71; N, 12.16. Found: C, 76.59; H, 6.76; N, 12.33. MS *m/z*: 345 (M^+). IR (KBr): 1550 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 8.44 (1H, dd, J=7.7, 1.5 Hz), 7.52 (1H, s), 7.46 (1H, ddd, J=7.7, 7.7, 1.5 Hz), 7.38—7.35 (2H, m), 7.30 (1H, ddd, J=7.7, 7.7, 1.5 Hz), 7.26—7.21 (2H, m), 7.19—7.13 (2H, m), 3.77 (2H, q, J=7.1 Hz), 3.60 (2H, q, J=7.1 Hz), 1.84 (3H, s), 1.28 (6H, t, J=7.1 Hz). ^{13}C-NMR ($CDCl_3$): 190.9, 167.7, 142.4, 141.5, 133.2, 130.9, 128.3, 128.0, 127.4, 126.0, 125.5, 125.4, 124.4, 90.6, 66.4, 44.7, 14.1, 8.6.

From the reaction of **7** (300 mg, 1.28 mmol) with *N*,*N*-diethyl-1-butynylamine (**11b**) (353 mg, 2.82 mmol), 1-benzoyl-2-diethylamino-3-ethylnaphthalene (**7a'**) was obtained as white prisms in 38% yield (162 mg) from the first fraction eluted with hexane, mp 85—87 °C (hexane). *Anal.* Calcd for $C_{23}H_{25}NO$: C, 83.35; H, 7.60; N, 4.23. Found: C, 83.41; H, 7.71; N, 4.16. MS *m/z*: 331 (M^+). IR (KBr): 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 7.82—7.71 (4H, m), 7.53—7.47 (2H, m), 7.42—7.29 (4H, m), 3.12—2.93 (4H, m), 2.80 (2H, q, J=7.3 Hz), 1.37 (3H, t, J=7.3 Hz), 0.94—0.36 (6H, m). ^{13}C-NMR ($CDCl_3$): 199.5, 146.0, 142.7, 139.3, 136.9, 132.8, 131.6, 130.0, 129.2, 128.8, 128.3, 127.3, 125.9, 125.5, 124.6, 48.4, 24.5, 14.8, 13.9. 1-Benzoyl-4-diethylamino-5-ethyl-2,3-benzodiazocine (**7b'**) was obtained as yellow prisms in 38% yield (200 mg) from the second fraction eluted with hexane/AcOEt=10/1, mp 142—143 °C (ether). *Anal.* Calcd for $C_{23}H_{25}N_3O$: C, 76.85; H, 7.01; N, 11.69. Found: C, 76.86; H, 7.09; N, 11.63. MS *m/z*: 359 (M^+). IR (KBr): 1540 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 8.41 (1H, dd, J=7.7, 1.5 Hz), 7.51 (1H, s), 7.46 (1H, ddd, J=7.7, 7.7, 1.5 Hz), 7.35—7.32 (2H, m), 7.30 (1H, ddd, J=7.7, 7.7, 1.5 Hz), 7.25—7.21 (2H, m), 7.18—7.15 (2H, m), 3.79 (2H, q, J=7.0 Hz), 3.52 (2H, q, J=7.0 Hz), 2.38 (1H, q, J=7.3 Hz), 2.19 (1H, q, J=7.3 Hz), 1.25 (6H, t, J=7.0 Hz), 1.02 (3H, t, J=7.3 Hz). ^{13}C-NMR ($CDCl_3$): 191.5, 167.6, 142.1, 141.8, 133.0, 130.9, 128.3, 128.0, 127.4, 125.9, 125.6, 125.4, 124.4, 97.9, 66.1, 44.7, 16.0, 14.6, 13.9

From the reaction of 1-chloro-7-methoxyphthalazine[9] (**13**) (300 mg, 1.54 mmol) with **11a** (377 mg, 3.39 mmol), 2-[4,6-bis(diethylamino)-3,5-dimethylpyridinyl]-5-methoxybenzonitrile (**13c**) was obtained as a pale yellow oil in 23% yield (133 mg). *Anal.* Calcd for $C_{29}H_{35}N_7O_8$ (picrate): C, 57.14; H, 5.79; N, 16.08. Found: C, 57.28; H, 6.01; N, 15.95. MS *m/z*: 380 (M^+). IR (neat): 2260 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 7.41 (1H, d, J=8.3 Hz), 7.18 (1H, d, J=2.4 Hz), 7.11 (1H, dd, J=8.3, 2.4 Hz), 3.87

(3H, s), 3.19 (8H, q, $J=7.1$ Hz), 2.19 (3H, s), 2.06 (3H, s), 1.07 (12H, t, $J=7.1$ Hz).

From the reaction of **13** (450 mg, 2.31 mmol) with **11b** (580mg, 4.63 mmol), 2-[4,6-bis(diethylamino)-3,5-diethylpyridinyl]-5-methoxybenzonitrile (**13c'**) was obtained as a pale yellow oil in 16% yield (150 mg). *Anal.* Calcd for $C_{31}H_{39}N_7O_8$ (picrate): C, 58.39; H, 6.16; N, 15.38. Found: C, 58.10; H, 6.32; N, 15.55. MS *m/z*: 408 (M^+). IR (neat): 2240 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 7.39 (1H, d, $J=8.8$ Hz), 7.24 (1H, d, $J=2.6$ Hz), 7.13 (1H, dd, $J=8.8$, 2.6 Hz), 3.97 (3H, s), 3.13 (4H, q, $J=7.3$ Hz), 3.10 (4H, q, $J=7.3$ Hz), 2.72 (2H, q, $J=7.3$ Hz), 2.60 (2H, q, $J=7.3$ Hz), 1.18 (3H, t, $J=7.3$ Hz), 1.08 (6H, t, $J=7.3$ Hz), 1.05 (6H, t, $J=7.3$ Hz), 0.78 (3H, t, $J=7.3$ Hz). ^{13}C-NMR ($CDCl_3$): 160.8, 158.4, 157.4, 151.6, 138.9, 133.1, 132.8, 131.3, 118.7, 118.2, 117.2, 113.7, 55.6, 48.2, 46.6, 21.3, 20.9, 14.8, 14.6, 13.9, 13.3

From the reaction of 7-methoxy-1-tosylphthalazine (**14**) (400 mg, 1.27 mmol) with **11a** (311 mg, 2.80 mmol), 3-ethyl-2-diethylamino-7-methoxy-3-methyl-1-tosylnaphthalene (**14a**) was obtained as colorless needles from benzene–hexane in 88% yield (444 mg), mp 78—80 °C. *Anal.* Calcd for $C_{23}H_{27}NO_3S$: C, 69.49; H, 6.85; N, 3.52. Found: C, 69.60; H, 7.03; N, 3.56. MS *m/z*: 397 (M^+). IR (KBr): 1300, 1155 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 8.13 (1H, d, $J=2.6$ Hz), 7.67 (1H, s), 7.58—7.53 (2H, m), 7.52 (1H, d, $J=8.8$ Hz), 7.14—7.11 (2H, m), 7.00 (1H, dd, $J=8.8$, 2.6 Hz), 3.80 (3H, s), 3.41 (2H, q, $J=7.3$ Hz), 3.29 (2H, q, $J=7.3$ Hz), 2.42 (3H, s), 2.33 (3H, s), 0.94 (6H, t, $J=7.3$ Hz). ^{13}C-NMR ($CDCl_3$): 158.1, 152.3, 142.9, 142.4, 135.9, 135.0, 131.9, 129.3, 128.9, 126.5, 126.3, 117.8, 104.3, 55.2, 49.1, 21.4, 20.4, 13.8

From the reaction of **14** (300 mg, 0.955 mmol) with **11b** (143 mg, 1.15 mmol), 2-diethylamino-7-methoxy-1-tosylnaphthalene (**14a'**) was obtained as colorless needles from benzene–hexane in 84% yield (330 mg), mp 84—86 °C. *Anal.* Calcd for $C_{24}H_{29}NO_3S$: C, 70.04; H, 7.10; N, 3.40. Found: C, 70.02; H, 7.28; N, 3.37. MS *m/z*: 411 (M^+). IR (KBr): 1300, 1140 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 8.08 (1H, d, $J=2.6$ Hz), 7.73 (1H, s), 7.56—7.53 (2H, m), 7.54 (1H, d, $J=8.8$ Hz), 7.12—7.09 (2H, m), 6.94 (1H, dd, $J=8.8$, 2.6 Hz), 3.76 (3H, s), 3.42 (2H, q, $J=7.3$ Hz), 3.37 (2H, q, $J=7.3$ Hz), 2.77 (2H, q, $J=7.3$ Hz), 2.28 (3H, s), 1.33 (3H, t, $J=7.3$ Hz), 0.97 (6H, t, $J=7.3$ Hz). ^{13}C-NMR ($CDCl_3$): 158.0, 152.1, 142.9, 142.4, 141.1, 133.4, 131.7, 129.4, 129.1, 128.9, 126.7, 126.2, 117.9, 104.3, 55.2, 49.6, 24.4, 21.4, 14.5, 14.1

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